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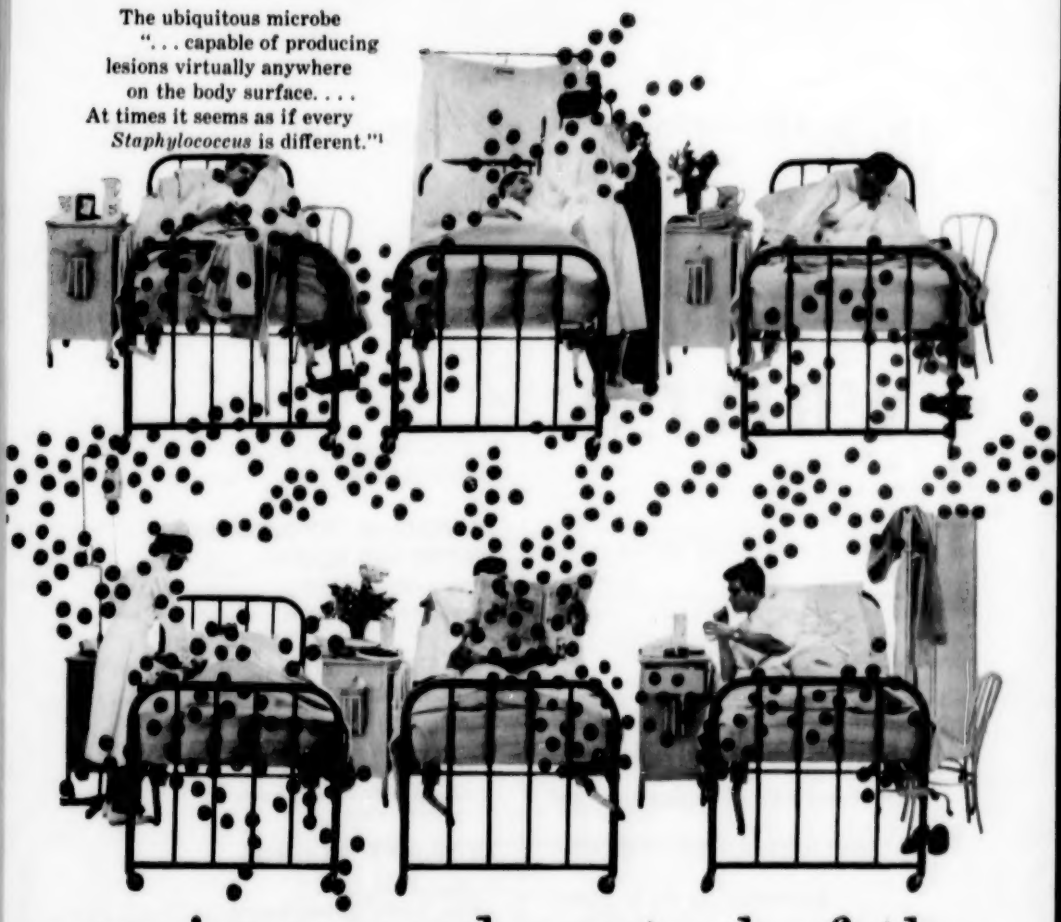

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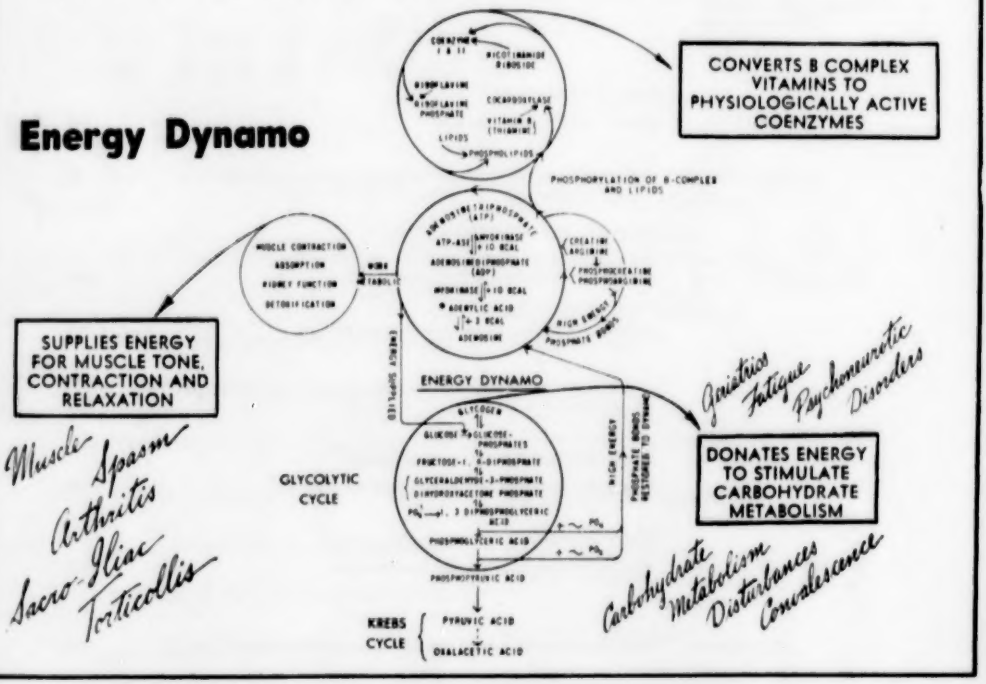

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Evaluation of Chlorpromazine in Psychotic Patients

A. Achaintre, P. Balvet, M. Beaujard, P. Broussolle, J. Perrin, F. Leveque, and A. Requet

LYONS, FRANCE

At the Psychiatric Hospital of Vinatier, in Lyons, France, we have been using chlorpromazine since 1953. Our early observations concerned only a limited number of patients, but several reports, French[1, 2] and Swiss[3, 4] in particular, prompted us to extend administration of the drug throughout our five departments, consisting of 1018 beds, and to appraise its merits after a clinical trial covering a full year.

Study 1

We believed that if a large patient population were treated with chlorpromazine, we would be able to judge better and more rapidly certain clinical characteristics and their relationships to therapy. This report sets forth our observations of the reactions of 530 psychotic patients.

MATERIALS AND METHOD

Our patients were distributed in the clinics, either open or closed, of five departments. Despite a few differences in conception among supervising physicians, conditions of observation can be regarded as similar for all patients, both male and female: the same environment, techniques, and processes for estimation of social readaptation applied to all.

The 325 women and 205 men studied showed the typical age distribution of psychiatric hospitals in France. Of the patients, 81 were between 20 and 30 years of age, 116 between 30 and 40, 145 between 40 and 50, 103 between 50 and 60, and 85 more than 60. Their diagnoses, classified according to the definitions of the *French Encyclopedia of Psychiatry*, published early in 1955, consisted of the following: 88 cases of hebephrenic catatonia; 38 cases of simple schizophrenia, schizomania in the sense used by Claude; 129 paranoiac psychoses; 18 varied chronic deliriums; and 17 paraphrenias. From these 290 schizophrenic processes, some psychiatrists might

exclude 10 paranoiacs, type Genil-Perrin, whom we have classified under chronic varied deliriums. We had, in addition, 83 cases of manic-depressive psychoses, distributed equally between depression and manic agitation; 33 chronic hallucinatory psychoses (French clinical definition); 31 cases of senile dementia (processes of involution, either arteriopathic or atrophic); and 38 cases of behavior disorders.

Of the cases treated, 34 had been evolving for less than six months, 119 between six months and two years, 103 between two and five years, and 270 for more than five years. We suspected that many of these chronic cases had been too hastily regarded as incurable. Previous therapies had been tried with 240 of the patients, including 93 Sakel treatments, 236 electroshock therapies, 76 pyretotherapy treatments, and 51 lobotomies. In all, 85 patients had temporarily responded, at least in so far as social improvement was concerned, but later relapsed, some soon after the discontinuation of therapy.

We have studied here the use of chlorpromazine, either in tablets or as sirup, and, very frequently at the start of treatment, intramuscularly or by intravenous perfusion. The average daily dosages were as follows: 130 patients received up to 100 mg., 294 patients received between 100 and 300 mg., 81 patients received between 300 and 500 mg., and 12 patients received between 500 and 1000 mg. Treatments were continued up to three months for 240 patients, up to eight months for 130 patients. No study lasted longer than 12 months, however.

In nearly half of the cases we administered various methods of psychotherapy or biologic treatments in conjunction with chlorpromazine. We employed Sakel comas in 27 cases, electroshock therapy in 103, hypnotic medication in 35, alternating therapeutics in 22, ergotherapy and sociotherapy in 279.

Evaluation of results is complicated by the fact that the social conditions to be found outside the hospital by patients whose psychoses had lasted more than five years did not allow us to discharge them, in many cases. Families, friends, and employers often neglect or otherwise dissociate themselves from patients after so long a period of hospitalization. This is more noticeable with women—only two thirds of our female patients experiencing recovery or considerable improvement could be discharged, whereas four fifths of the men were able to leave the hospital. A man's having a trade to re-enter seems to facilitate his social readjustment in conditions of modern France.

Our evaluation of results is as follows: Recovered—attenuation of the psychopathic process sufficient to permit discharge from the hospital and return to normal occupations. Much Improved—adaptation to environment inside the hospital, but not sufficient for discharge. Improved—varying degrees of progress in conduct within the hospital routine. Not Improved—absence of any noteworthy changes in attitude or behavior.

RESULTS

Table I shows the results of our treatment in the various diagnoses. We actually released 101 patients; we deferred or decided against discharge in 36 cases where outside conditions would have been unfavorable, although we regarded the patients as recovered.

Our principal success was achieved with schizophrenic patients, 72 per cent of the 137 recoveries being among that group. Chlorpromazine seems to attenuate the pathologic process considerably and permit subsequent attempts at readaptation and resocialization of the patient. Ten of these improvements, or 7 per cent of the total, were among patients suffering delirious episodes. Twenty-five per cent of the recoveries were among patients with all types of manic-depressive psychoses. We believe we had greater success in cases of depression than in mania, but further investigation of this is necessary. The duration of treatment in manic-depressive patients does not generally exceed four months, except in a few patients treated for at least eight months. It seems that in the shorter period we have done little more than give a symptomatic relief of a manic or depressive attack, without being able to decrease its duration, whereas in the longer treatment we have been dealing with chronic manias or melancholias. However, our case load in this diagnosis has not been great enough to permit valid conclusions.

We noted only four relapses during and six after treatment in the total group of 137 patients who recovered. However, a longer period of study would be necessary to record accurately the extent or individual effect of these relapses.

TABLE 1

Chlorpromazine Treatment of 530 Patients (Study I)

Diagnosis	No. patients	Results			
		Recovered	Much improved	Improved	Not improved
Hebephrenic catatonia	88	24	21	36	7
Paranoiac psychoses	129	32	43	48	6
Simple schizophrenia	38	7	15	13	3
Varied chronic deliriums	18	6	5	6	1
Paraphrenias	17	4	8	5	1
Manic-depressive psychoses	14	7	1	5	1
Manic	34	14	12	7	1
Melancholia, depressive	35	13	14	8	0
Confusion	6	2	2	2	0
Delirious episodes	16	10	2	3	2
Chronic hallucinatory psychoses	33	8	8	14	3
Senile dementia	31	0	4	23	2
General paresis	7	1	1	4	1
Epilepsy	9	0	3	5	1
Alcoholism	3	0	0	2	1
Anxiety	5	2	0	3	0
Behavior disorders	38	9	19	19	1
Total	521*	139	158	203	31

* Medication was withdrawn from 9 patients because of side effects.

We rated 149 patients much improved. For most diagnoses the numbers of recovered and much improved patients corresponded. We considered 226 patients to be only improved or not improved. Of this group, 53 per cent had been classified as schizophrenics, 11 per cent as manic-depressives. Failures occurred noticeably in cases of senile dementia, behavior disorders, epilepsy, and other conditions statistically insignificant. Regarding senile dementia, we observed that, while chlorpromazine seemed to offer only slight improvement, the patients were brought back by it to an acceptable level of life. However, we found that great precautions must be taken in administering the drug to delicate patients.

Although recoveries were achieved at every dosage level, we concluded that the average maintenance dose is between 100 and 500 mg./day. Oral administration of 300 to 500 mg. daily has provided the greatest number of recoveries. We had too few patients treated with more than 500 mg. daily to form judgments. Treatment begun intramuscularly or, when isolation was possible, by a series of intravenous perfusions of 50 to 100 mg./day was followed by oral administration.

We have purposely omitted description of the generally improved atmosphere within the hospital as a result of chlorpromazine treatment. Many patients whom we evaluate as improved have actually become much more manageable, and this fact has indirectly affected other patients. Greater efficiency and ease of operation have been made possible; this phase of our work is the subject of a forthcoming thesis by one of our interns, M. Lauxerrois.

CONCLUSIONS

In general, and particularly in certain diagnoses, our results were encouraging. We concluded that prolonging treatment in established psychoses definitely offers promise of success in certain kinds of disturbances. We believe also that considerable benefit might be found in the use of electroshock therapy and ergotherapy as alternating therapies with chlorpromazine. The physician, with whatever facilities are at his disposal, must take advantage of the slightest benefit induced by the drug to bring about in the patient a certain degree of readaptation; from there, prolongation of treatment will enable the patient to reach increasingly higher levels of adaptation. If we want to increase the good results and if we want to study still more objectively the effects of this drug, we must adopt a psychiatric attitude, avoiding its indiscriminate application.

Chlorpromazine seems to be far more effective in psychoses that have not progressed too far, but it also enables the physician to reach long-established patients who previously have been too readily considered incurable.

During the full year of our study, recoveries were achieved most frequently in either the first three months, which do produce the best and most numerous results, or the last four months, which show a definite increase in recoveries over the middle period. Although the chances of success and the number of good results seem to decrease in prolonged psychoses, they rise a second time, after an intervening period of poor results.

This leads us to an interesting observation: *the longer the psychosis has lasted, the*

more necessary it is to prolong treatment because remission is more slowly achieved in psychoses that have been present for longer periods of time.

Considerable improvement, at least, appears to be a reasonable expectation in psychoses evolving for two to five years or longer when medication is prolonged. Thus, hope can be retained for mental patients considered in the chronic group.

Furthermore, an argument supporting our opinion can be found by examining results with patients who had shown remission on previous therapies, but had relapsed. Of the 85 patients with such histories in our study, 33 achieved recovery with chlorpromazine, even though half of these relapsed patients had been ill for more than five years. In our series, chlorpromazine brought about recovery in one third of relapsed patients and in one fourth of those failing to respond to other therapies.

The drug brought about recovery in 26 per cent of our patients and varying degrees of improvement significant in hospital atmosphere and routine in 60 per cent of the cases.

For certain schizophrenic processes and manic depression, chlorpromazine appears to be an almost specific therapy; 28 per cent of the schizophrenics and more than 50 per cent of the manic-depressive patients achieved recovery. Patients with delirious episodes and with acute mental confusion seemed to respond well to four months of chlorpromazine treatment.

For a given diagnosis the percentage of recoveries decreases as the age of the patients increases. Belated recoveries are obtained in schizophrenia; however, advanced age in a patient often carries with it long-standing psychosis or a dementia process caused by involution, on which chlorpromazine did not seem to have any considerable effect.

That the drug is effective in combination with other treatments is indicated in our recovered patients, 5 per cent of whom were given a Sakel treatment, 20 per cent electroshock, 6 per cent hypnosis treatment, and 60 per cent ergotherapy and sociotherapy, associated with chlorpromazine. Patients receiving ergotherapy and sociotherapy constituted more than half of our recoveries; however, there was only 30 per cent success in our patients undergoing these complementary treatments. We interpreted this phenomenon as resulting, first, from the fact that certain processes do not respond to chlorpromazine. We realized, second, that because of a lack of facilities our methods had not been sufficiently individualized to make the combination of chlorpromazine and individual therapy (psychotherapy, ergotherapy, or sociotherapy) give optimum results. We concluded that benefit could be obtained by combining chlorpromazine with two other treatments, electroshock and ergotherapy, as alternating therapies.

In addition to the administration of chlorpromazine, we consider it useful to associate psychotherapeutic contact and maintain it constantly for several months after the patient has left the hospital.

Study II

While the drug did not seem effective in senile dementia and required a longer

TABLE II

Chlorpromazine Treatment of 56 Patients (Study II)
(Results in Relation to Clinical Characteristics, Including Age, Duration of Psychosis, and Diagnosis)

	Patients (56)	Recoveries (35)*
Age		
20–30	18	11
30–40	17	12
40–50	9	6
50–60	10	5
More than 60	2	1
Duration of psychosis		
6 months	20	19
6 months–1 year	5	3
1–2 years	5	2
2–5 years	7	6
More than 5 years	19	5
Diagnosis		
Schizophrenia	22	11
Depression	17	13
Mania	7	6
Delirious episodes	3	2
Epilepsy	3	
Paraphrenia	1	3
Alcoholism	1	
Behavior disorders	2	

* Thirty of these patients were actually discharged.

period of administration in older patients, we were satisfied that results could be obtained with patients previously regarded as incurable. In the previous series (study I), 51 per cent of our patients had been ill for five years or longer, 71 per cent for two years or longer. The relatively poor response to ergotherapy and sociotherapy as complementary treatment with chlorpromazine prompted us to make a more intensive study of this combination with younger patients.

With them we hoped to demonstrate the validity of our clinical impressions that the drug is very effective in the first three months of treatment, in recent psychoses, and in initial treatment. We also hoped to take advantage of improved facilities in a new section of our hospital, so that we could more effectively consolidate each patient's gains, however slight, with ergotherapy and sociotherapy at the earliest possible time. With the case load reduced from 530 to 56 for this study, we were able to individualize the therapies to a much greater extent.

MATERIALS AND METHODS

Thus, in the new department, under Dr. Requet, we conducted a second five-week

study. In this department facilities favor rest, the rooms having one or four beds. With dosage regulated according to the patient and his physical condition, we relied chiefly on oral administration. As table II shows, most of these patients were between 20 and 40 years of age; most of the psychoses had been evolving either for less than six months or for more than five years. Schizophrenic and depressive patients again were more numerous than other types. Seventeen were relapsed patients, previously discharged from hospitals after other treatments. In 37 cases the average daily dosage was maintained at 300 mg. or less; in only 4 cases did it exceed 500 mg. daily.

We retained oral administration as our standard practice, but found some particular uses for intravenous perfusion. Nineteen of the patients were given intravenous perfusions, receiving 50 to 100 mg. once or twice daily; a liquid dose was given during the afternoon and in the evening. However, perfusion seems to be valid only under certain conditions of administration, when the patient feels secure in a room or small dormitory and can be calm, in semiobscurity. Only thus can he become sufficiently relaxed to sleep. Experience has led us to use intravenous perfusion increasingly often, especially when the patient is brought to the hospital in an acute state, but it is used only in this new department. In our hospital, intramuscular administration is virtually a thing of the past. We give chlorpromazine orally, in tablets or in sirup form.

RESULTS

Results were proportionately even more encouraging than in the previous series (study I). Recovery was achieved by 62 per cent of this group. Dramatically, chlorpromazine and the complementary ergotherapy and sociotherapy produced recovery in 95 per cent of the patients with recent psychoses, in 26 per cent of patients ill for five years or longer. We noted recovery in 11 of the 22 schizophrenics, 13 of the 17 depressives, and 6 of the 7 manics. Results in relation to age, diagnosis, and duration of psychosis are shown in table II.

In 1955 chlorpromazine enabled us to bring about a greater number of improvements: adaptation either to the activity of the department, when acceptable conditions of life exist, with the possibility of recreation and working in a shop, or to the activities of the hospital, with attempts at sociotherapy through a moderate cultural program, including dances, movies, and dramatic presentations. Each patient has his treatment. Soon he becomes interested in working in our shops during the afternoon.

During the last five months regular consultations with recently discharged patients have been attended by 90 per cent of those registered. In a few cases we have been able to discharge patients prematurely. Treatment has been continued on an outpatient basis, with the patient returning for consultation; all continue to improve.

CONCLUSIONS

In summarizing this latter study, we wish to stress the fact that chlorpromazine brings about more rapid recoveries. This is highly significant, since the time a

patient spends in the hospital is, in itself, a factor of desocialization. Otherwise our conclusions are almost exactly parallel with those in the previous study. Schizophrenia is the best indication for chlorpromazine; young patients are more rapidly improved; recent psychoses are more readily improved; psychoses of long duration can be treated with some success, regardless of previous treatment. However, we have found considerable differences between the results obtained by treatment with chlorpromazine in recent schizophrenias, long-established schizophrenias, and manic episodes.

In recent schizophrenias the psychiatrist easily senses the existence and the virulence of the fundamental dissociative process underlying the clinical syndrome. From the onset of treatment, which is effective in the vast majority of these cases, this virulence seems to become attenuated to such a point that family and medical contacts are established and the patient no longer manufactures secondary symptoms; it is as though he no longer needs them. Yet, the physician still senses the existence of the fundamental disturbance for a considerable time.

Conversely, in longer established schizophrenias there exists, to begin with, a kind of cooling of the affective tonality of secondary symptoms. Then they seem to dry up, as though they were no longer fed. At last, social contact is re-established, and the patient reveals once again his authentic personality.

In typical manic episodes there is a simple braking of the symptomatic exuberance, which is nevertheless most interesting since it permits, in most cases, hospitalization of patients without restraint—just as though these manic episodes had become abortive episodes.

Like streptomycin in tuberculosis or phenobarbital in epilepsy, chlorpromazine given in individualized doses is for us today the basic drug. We have barely used associated physiotherapies and chemotherapies in this latter study—only one Sakel and one electroshock. We expect even better results with further improvement in organization and facilities. Generally, chlorpromazine rapidly brings about a true recovery or at least a really effective human contact, real prophylaxis of mental disease. Were the psychiatric hospital equipped like a general hospital, we believe that we could now achieve real psychiatric remission on a broad scale.

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SPECIAL ARTICLE

What I Have Learned in Life

Roger I. Lee, M.D., *author of this paper, was born in Peabody, Mass., in 1881. He attended Harvard College and Harvard Medical School, receiving his M.D. degree in 1905. In 1907 he went into private practice in Boston, and in 1918 was given the position of Visiting Physician at the Massachusetts General Hospital. He served as Henry K. Oliver Professor of Hygiene at Harvard from 1914 to 1924, returning to practice in 1924. During World War I he served in France with Base Hospital 5 and as Medical Consultant to the Third Corps, and was gassed during the Argonne attack. He was president of the American College of Physicians in 1941; chairman of the board of trustees and president of the American Medical Association; president of the Massachusetts Medical Society; and a member of the Association of American Physicians, the Society for Clinical Investigation, and the American Academy of Arts and Sciences. His book,* The Happy Life of a Doctor, *was published last year; he is also the author of* Health and Disease *and coauthor of* The Fundamentals of Good Medical Care. *He now lives in Brookline, Mass., and is continuing in private practice.*

The first thing I learned in life is very prosaic: the value of work. Medicine has always seemed to me a dedicated profession. In a sense, a medical student takes a sort of veil, especially in his interning years. Even in later life we had a kind of motto in our home: a physician may be away or dead; there are no other excuses for his not being available. Once I had a mild case of pneumonia. A patient called on the telephone and was told I was ill. Nothing daunted, he came to our home, asked the maid where I was, and came upstairs to find me in bed. He stated his problems, received his answers, and then went his way. Now my devoted dog put himself on guard at my door, and he would not come into the room until he was satisfied that I was well. But patients and dogs are different. Besides, there is an ancient custom that if the physician dies, the bill does not have to be paid.

I was once on a committee to investigate complaints against physicians. The husband of a patient complained that a certain physician had refused to come to see his patient. When I questioned the physician he was at first puzzled. Then he

This article is the first in a series of contributions by eminent physicians on "What I Have Learned in Life."

told his side of the story. It was a snowy night and he had just come in after an obstetric case. The patient had had a carbuncle on her neck for 10 days but had done her housework. The husband insisted that the physician come at once to see her. Reluctantly, he agreed. He told the husband that, as was the custom, he, the physician, would get behind the town plow, go to a certain corner a quarter of a mile from the house, and wait for the patient's husband to pick him up, as the plow did not go up that road. "What!" shouted the husband, "I wouldn't send a dog out on a night like this." The physician did not go. Along similar lines, a friend of mine once published "The Midnight Ride of Roger Lee," a waggish account of the two of us pushing a car most of the way from Concord to Newport, New Hampshire, one snowy night.

I am inclined to include skepticism and caution as some things I learned early in life. But as antidotes against excessive skepticism and caution I would include enthusiasm and curiosity. Incidentally, a sense of humor is always helpful in giving taste and relish to the mixture of our attributes.

It is true, I think, that most people including physicians learn more readily from the spoken word than from the written word. The ability to learn from the written word, i.e., the medical literature, is an almost indispensable asset for a physician. It can be acquired with practice by every physician. It is, of course, far easier to indulge in inaccuracies in the spoken than in the written word. I have long been an advocate of conversing with speakers and writers of papers at medical meetings. You can then form an opinion of the man and decide (1) if it is worth while to hear him speak and (2) how much caution is necessary after hearing or reading his articles.

The president of a medical society made an illuminating, even if devastating, comment on an address before the Society. He said, "Gentlemen of the Society, we have just listened to a very interesting talk and I want to assure you that while it was all interesting some of it was true."

The late Hans Zinsser once lamented that he had never made a "bull's eye" in his life of medical investigation. He went on to say that he had seen numerous "bull's eyes" made, not infrequently by someone who was looking elsewhere while fingering the pistol in his pocket, which went off by chance and hit the "bull's eye."

A wealthy philanthropist had given a large sum of money to a medical school. At the dedication of some new buildings, the philanthropist was approached to endow a building for medical research. The philanthropist replied, "Why not have someone invent a patent medicine. That is the most remunerative business I know." Even the president of a great university publicly stated that the deficit of the medical school could easily be met by revenue from a few patented medicines. Indeed, some universities have profited by patents on medical products. It was argued that a professor of physics might take out a patent on a process related to submarine signals, for example, and secure a considerable income for himself. But the point is that by common consent inventions related to therapeutics and the public health are ethically different. What would happen if the holder of a patent tried to get a monopoly on a curative serum or other substance in an epidemic! To be sure, the patent on insulin has been administered very wisely, but the participants in the patent have profited greatly. It has seemed to most reasonable men that universities and university

employees ought not to profit by such patents. If, because of the weakness of the United States patent system, some protection of the public should be assured, this protection could be accomplished if universities took out patents and dedicated them to the public. For example, a patent was secured presumably for a serum against scarlet fever. As issued by the United States Patent Office any person working with any strain of *Streptococcus* would have to get a license from the holders of the patent. Some persons with just an ordinary curiosity in regard to the *Streptococcus* were threatened with a suit for $50,000, certainly a situation fraught with the dangers of monopoly and despotism. The situation is not now entirely clear but there is a growing feeling that patents related to therapeutics and the public health ought not to be profit-bearing to universities, hospitals, and the medical profession. Of course, business loves patents with profits.

No less an authority than the late Dean of the Harvard Divinity School noted the fact that among all the professions, the medical profession alone has worked under the same code of ethics for more than 2000 years: the famous Hippocratic oath. Hippocrates was the humble Greek physician who devoted himself to the unselfish practice of medicine, in contrast to the arrogant academicians in ivory towers who indulged in idle speculation such as how many angels would stand on the point of a needle. Of course neither the Dean nor myself would or could argue that this code of ethics has been constantly maintained, certainly not in the Dark Ages. It functions perhaps as a conscience rather than an oath of office.

We hear a lot of talk that advances in medicine will enable man to live to great age. This is sometimes referred to as the Medical Millennium, which is of course very silly. My grandfather, an irascible retired newspaper man, who died in his eighties, always claimed that he was approaching his personal millennium when he needed but two books to keep him happy. His millennium would be when he needed only one book; he would have forgotten the first part of that book by the time he had finished it and thus could read with interest and excitement the same book over and over again. But he never quite achieved the millennium of one book.

It is of course true that so-called civilized people are living to a greater average age than ever before. But the proportion of men or women who reach 100 years of age has not increased. To be sure, infantile mortality has been tremendously reduced; in other words, the delicate babies who once died now live to adult life and even beyond 70 years of age. But if one aspires to live to 100, one must choose his forebears with a great deal of care, for the really long-lived people have ancestors who were also long-lived. Some years ago the first health officer of New York City was about to have his one hundredth birthday. The American Public Health Association wanted to celebrate it with a dinner, the implication being that he achieved his age by virtue of having practiced his profession of health officer on himself. At first I was opposed to the celebration because I felt it might make the old man ill, but then I decided it wouldn't make much difference anyway. So we gave him the dinner. I was mean enough to talk to him about his ancestors. He didn't like that very much because he had numerous ancestors and collaterals who lived to be 90 or 100. He then turned my attention to his daughter, who took care of him. Now nearly every really old person tends to attribute his longevity to something that he does or

eats. The oldster tends to think it was because he took exercise or took no exercise, or that he smoked or didn't smoke; he lived to be old because of something that he himself did, not because of his ancestors. The ex-health officer's daughter was cautious and noncommittal, until I asked her what she fed the old man. She smiled, a bit grimly I thought, when she answered "milk, whisky, and flattery" and added that "the last two seemed the most important." My personal preference is for the last item, flattery, as the best food for the aged.

I hasten to say that I believe with enthusiasm in modern antibiotics and the other so-called miracle drugs. They certainly prolong life, but not past 100 years in most cases. I recall vividly a physician friend who was perhaps 10 years older than I; he was a bachelor and lived alone. Finding him unconscious with pneumonia, I took him to the Phillips House, a department of the Massachusetts General Hospital, where he received the appropriate antibiotic drugs. The next morning I found him somewhat groggily trying to read the newspaper. His temperature was normal and he was certain of recovery, and I was not prepared for this blast, "Darn you, Roger, I was all prepared to die. You drag me back, and now I've got to do it all over again." Which he did a few years later, after neglecting a cancer until it reached the inoperable stage. Now I would save him again if I had to do it over. Most people want to live and hang on to life with tremendous tenacity, but this one man was an exception.

Speaking technically, the antibiotics, in appropriate cases, cure the disease. But the prevention of disease is still the ideal. The administration of typhoid vaccine, as devised by Sir Almroth E. Wright, prevents typhoid fever in the civilized portions of the world; the use of shoes has largely obliterated hookworm from our southern states. We are struggling to eliminate a particular kind of mosquito that is the only method of the transmission of malaria. The ambulatory male malaria patient tends to take his quinine with a common spoon from a bowl at the end of the bar, when he gets his whisky. He may stay alive but this is not the scientific method of curing or preventing malaria.

The history of medicine contains many tales of drastic treatments and the direct opposite. In all probability, from the bleeding, blistering, purging, and puking days came homeopathy. But some patients like drastic therapy, while others prefer gentle treatment. Of course it is the same in bringing up children, e.g., the theory of "spare the rod and spoil the child," usually with the added insult to the child, "This hurts me more than it does you." It has been reported that some people, even soldiers, like compound cathartic pills, if not prescribed too often. Physicians have lost many patients because they did not give either some medication or a prescription. Diet and rest were all right, but the patient insisted on getting a prescription in return for the physician's fee. About 100 years ago the Massachusetts General Hospital made whisky, liniment, popular tonics, cough medicines, and the like. The Hospital even made ink. Once a large batch of ink turned yellow, and one of the physicians suggested that it might be made into a liniment by the addition of chloroform, salt, and other things. It then had the requisites of a popular liniment, or of any medicine in fact, namely, color, smell, and a sense of irritation where applied. It was called "linimentum sali." Today "linimentum sali" cannot be

obtained at the Hospital apothecary but it still has a popular sale in the drug stores near the Hospital!

I was brought up, so to speak, on two doctrines: (1) the nil nocere doctrine, that is, do no harm to your patients, and (2) the doctrine of the self-limitation of many diseases. Dr. Oliver Wendell Holmes, Professor of Anatomy at the Harvard Medical School, was an ardent advocate of the theory of the self-limitation of disease. The ordinary cold is a self-limited disease. Of course it is necessary to make sure that it is the ordinary cold. Holmes maintained that if physicians and their patients accepted the doctrine of the self-limitation of disease and threw all the products of the pharmacopoeia into the sea, it would be a great boon to the human race.

I have always believed that it is not only wise but necessary for a physician to examine the patient. Incidentally, the patient usually likes to see the physician and have him take his pulse and look at his tongue. I know that some doctors want to see only the data, the electrocardiogram, the chemical tests, and the roentgenograms. As a skeptic, I can report that switching labels is possible, and as a cynic, I can report that some tests, if properly carried out, are accurate, but other tests are better called approximations. After I was gassed in World War I, the roentgenogram of my chest showed extensive metastatic cancer of the lungs. Today the roentgenogram is the same, but I am alive after more than 37 years. An eminent roentgenologist, an intimate friend of mine, begged me never to have any more roentgenograms made of my chest. He had tears in his eyes when he reported on the roentgenograms because he was fond of me and also because he realized that the roentgenograms to which he had devoted his life had let him down.

Many years ago, when the Wassermann test was first publicized, I undertook to try it with the idea of incorporating it into the routine of the Massachusetts General Hospital. I could see no objection to using a different hemolytic process, but I found that this was considered a crime. I then came to the further conclusion that the antigen did not have to be a syphilitic liver and therefore the test or reaction was not absolutely specific. Of course, we now know that if a patient has pneumonia, he will probably have a positive Wassermann test, and there are other conditions that give a positive Wassermann test. The Wassermann test is not specific, but it is fairly reliable in the absence of most obvious diseases. And my conclusion was a blow for caution, skepticism, and perhaps cynicism.

I was interested in primary pernicious anemia in the days before liver therapy. An important part of the therapy of primary pernicious anemia was the elimination of protein from the diet because in this form of anemia, hydrochloric acid was uniformly absent from the stomach. It was another victory for healthy skepticism when it was found that liver (a protein) by mouth could control pernicious anemia.

The late Sir Alexander Fleming, who developed penicillin, always insisted that it was an accident: a mold got into a culture of some of his bacteria and the bacteria promptly ceased to grow and died in any proximity to the mold. I always insisted that molds had fallen into growths of bacteria as long as we knew bacteria but that it took a genius to recognize what was happening. We both were appalled at the possible harm penicillin might do. I gave a patient penicillin for a throat condition caused by streptococci. She promptly got much better, but I was startled to see a

long black beard in her throat, which caused no symptoms. The penicillin had killed off the streptococci, and the molds, kinfolk of penicillin, had moved in. We now know that if penicillin is administered too long, an intestinal bacterium, the enterococcus, which we have always considered entirely innocuous, may suddenly begin to grow and to acquire toxicity and may indeed kill the patient. Probably few persons will take enough penicillin to kill them, but I worry about it. Dr. Koussevitsky, the late gifted leader of the Boston Symphony Orchestra, was always bothered by a sniffle in his nose. He wanted treatment and especially treatment with the new miracle drugs. I refused him and he felt aggrieved. One day, after a trip around the country with the Orchestra, he came to my office and disclosed a very bad rash. He had persuaded a physician in another city to give him penicillin. I have seen deaths due to the "miracle drugs," but only rarely due to penicillin. Of course, you may say, "Oh, most of these drugs are really harmless, and perhaps you are trying to get more work for the physicians. But disregarding the antibiotics, have you any idea as to the number of people who take a barbiturate when they ride in a sleeping car or an airplane? Barbiturate habit is a common thing, especially among women. The most popular drug sold semi-illegally over the counter to men only is the male hormone, in other words, some form of testicular extract.

I have deliberately cited some of the bad features of the so-called miracle drugs, including of course the antibiotics. I have already ventured to suggest that it is more effective to prevent a disease by vaccination, as in the case of typhoid fever, which in the Spanish-American War killed a thousand soldiers to one soldier killed by a bullet. Vaccination against smallpox is almost miraculous in its prevention, but nothing is always perfect.

Mankind has always been interested in eating and drinking. To most people a dog is a dog, even when comparing a greyhound and a mastiff, both of the same length or height but very different in weight. For mankind there are standard tables for weight for different ages, height, and sex but with no allowance for build. It must be said that ideals have changed since the days of Venus de Milo, who was certainly overweight by today's ideals. The idealists are terribly bothered by women's knock-knees. This is of course purely physiologic as the child-bearing woman needs a bigger and wider pelvis than the man. A middle-aged woman who boasts of her perfect weight probably has very thin legs, a small pelvis, and a wrinkled face and neck. Of course, by this time it must be obvious that I am prejudiced because of my weight. Should I not be ashamed of my obesity? Probably. My excuse? When I was thin, I was sickly; when I put on weight, I felt well. This is always greeted by hoots of derision and shouts of "special pleading," even when I explain that my exercise is limited because I am a busy physician and because I was gassed in World War I. I gave up trying to emulate Apollo years ago, and I turn to Shakespeare's, "Yon Cassius has a lean and hungry look." And isn't a devil always depicted as thin? To be sure, the Hollywood experts claim that a woman is more photogenic when she is 10 per cent under her standard weight.

Among our most distressing faddists are the food faddists; for example, those who chew food a hundred times. One wonders if these people ever had a dog and watched him gulp his food. And there is the bowel perfectionist, whose life centers on his

bowel movements in his old age, just as at 20 he thought only of girls and at 40 thought only of business.

Now we all grant that man is living longer because he escapes early death by better hygiene and better sanitation, aided by vaccination, the use of antibiotics, and better medical care. But the result is that we are creating a new and difficult problem: the problem of geriatrics, the care of the aged. Then too, men are subjected to compulsory retirement at a much earlier age, thus involving old age pensions, compulsory retirement pay, and many other factors. When he was 70, the late President Lowell of Harvard warned that if the training of men kept on being prolonged and the retirement age of men kept on being lowered, perhaps some men might be retired before they were trained. Anyway there is a rapidly increasing problem of old people. They can't all be put in old people's homes. And curiously enough, the unhappiness of the old is not primarily financial. It is rather a feeling of uselessness. Their egos do not take kindly to sitting on the shelf waiting for death.

If you have borne with me this far, you will see that medical advances have resulted in better sanitation, better hygiene, better health through childhood, and longer lives, but within a restricted range. There is no medical millennium of years added at the top of old age. A great philosopher, Claude Bernard, brushed aside Pasteur, bacteriology, vaccines, sera, antibiotics, and miracle drugs as factors in the real prolongation of life. After all, medicine is a new profession and a new science despite the fact that it has reasonably kept its moral code for more than 2000 years.

It must be remembered that men have fought, bled, and died during all of history. Today, due to use of airplanes and atomic science, we have deadlier weapons. It must be remembered that there were vehicular accidents before the advent of automobiles. Also, before the days of Alcoholics Anonymous men died from alcoholism. And when the discovery of America led to that stupendous exchange by which America received smallpox from Europe and Europe received syphilis from America, it was merely an example of the fact that transportation leads to the spread of disease.

There are those who speak glibly of improving on nature. And here are we, relatively speaking, a few specialized individuals on a small secondary planet and only recently aware that there are many worlds, most of them much larger than our small solar system, of which we know little or nothing. We do not know why certain salmon swim several thousand miles back to the place of their birth in order to spawn and die. And what tells them how to get there? To be sure, we have learned how to protect airplanes by the study of bats who fly safely through wires that they cannot see. The young women of today would like to emulate the hen and lay an egg every now and again, rather than go through a nine month pregnancy. But do we know enough to "candle" the eggs? We can now get along without certain portions of our brain, but we have to be very careful and very precise as to what portions of the brain we discard. Nature makes some things that we can do without: an arm, a leg, a breast, a sexual gland, or even one kidney, one eye or one ear, the spleen, the stomach, or a part of the bowels. But so far, we cannot make these organs. We can give a patient a new cornea for his eye, but we cannot give him a new eye. We cannot make a new kidney, stomach, or brain; the patient has to get

along with what he has left, although he can do pretty well on a borrowed kidney, among other possible replacements. But medicine still concerns itself with patchwork, and medicine is not yet a science, although it is becoming so.

It seems at this date that out of the science of medicine may come developments and discoveries that may possibly delay the deterioration of man, continue his usefulness to a later date, and thereby actually prolong his effective life as he lives longer. But unless our laws relating to retirement, pensions, and the like change, it will be a terrible day for taxpayers.

Medicine possesses today, as it always has, a universal language, although it is not recognized as such even today because of the segregation of nations and races. Disease is cured and prevented in the same way all over the world. Malaria and scurvy, for example, are precisely the same, north, east, south, and west. Therein lies the great potentiality of medicine.

At this time, in these days of stress and misunderstanding, it seems very evident that there is no common religion in the nations of the world, nor is there any common law. Art, music, and medicine stand apart as being universal throughout the world. They are the same everywhere. Perhaps business, the most recent of the professions, may find its way, despite the present artificial barriers, to a place of a universal activity, irrespective of language and localized prejudices. That is a consummation greatly to be desired. Perhaps medicine and business can together bring an understanding and a universality that may cure a troubled world, now so full of misunderstandings, suspicions, and the belief that only war can settle its troubles. Today there is no place further than a day's journey by air. We are at least all neighbors. We pray that tomorrow the reward of a universal profession will be peace in the world.

SYMPOSIUM ON MEDICINE AND WRITING

The Symposium on Medicine and Writing that appeared in the November 1956 issue of INTERNATIONAL RECORD OF MEDICINE has been published this month as a Monograph. The articles included in this Monograph are: "The Editing of a Modern Medical Textbook" by Russell L. Cecil; "Plain Talk and Clear Writing" by Morris Fishbein; "The Principles of Bibliographic Citation" by John F. Fulton; "The Art of Communication" by Joseph Garland; "On Writing a History of Medicine" by Douglas Guthrie; and "Minerva and Aesculapius: The Physician as Writer" by Félix Martí-Ibáñez.

This 72 page Monograph is sold for $3.00. As the fourth in the series of MD International Symposia, this book is the companion piece of *Medical Writing*, which was published in May 1956.

To obtain this monograph, write to MD Publications, Inc., 30 East 60th Street, New York 22, N. Y.

Antibiotics and the Problem of Medical Communication

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ANTIBIOTIC KNOWLEDGE IN TIME AND SPACE

From our various fields of clinical research and practice, we are gathered here for our Fourth Annual Symposium, the object of which is to assess what progress has been made during the past year in the field of antibiotic and chemotherapeutic drugs, to consider a number of as yet unresolved clinical problems, and to outline prospects for future research. These Symposia, which started as a national experiment, have become, thanks to your efforts and work, an international institution yielding year by year an ever-increasing and bountiful harvest of rewarding discoveries.

If we look back at the three preceding symposia and anticipate the one starting today, we can see the result of our efforts in the following figures: 580 papers; 43 new antibiotics; and more than 3600 printed pages covering the work of 1437 writers of 35 different nationalities. These figures reveal with the cold eloquence of all statistics how these Symposia have greatly increased the already considerable *corpus doctrinalis* on antibiotics, which has been growing ever since that memorable day when a patient scientist kept his rendezvous with destiny in his humble laboratory at St. Mary's Hospital in London and made the discovery that was to change the whole face of modern therapeutics.

Never before in the history of medicine has there occurred a case comparable to this one, in which the collaboration of clinicians and research workers devoted to the study of a single group of curative agents has produced such a monumental body of knowledge and learning. If we remember that work in other fields of therapeutics, such as alkaloids, vitamins, hormones, and sera, was developed in its beginning by isolated individuals, and later by team work, but always in a sporadic and disjointed way both in time and space, it might strike us as remarkable that in barely fourteen years colossal progress has been made in the knowledge, research, and clinical use of as new a family of drugs as the antibiotics. This has been attained not only in time, by forcing the pace, thanks to the ever-increasing rhythm of work, of the stages of medical history, but also in space, by conducting the study of antibiotics on an international scale unprecedented in the evolution of medicine.

The headlong "vertical" progress—in time—of this work is supported by its tremendous "horizontal" expansion—in space—the result of which has been that

Presented at the Fourth Annual Symposium on Antibiotics, Washington, D. C., Oct. 17, 18, and 19, 1956, sponsored by the U. S. Department of Health, Education, and Welfare, Food and Drug Administration, Division of Antibiotics, in collaboration with the journals ANTIBIOTICS & CHEMOTHERAPY and ANTIBIOTIC MEDICINE & CLINICAL THERAPY.

antibiotics are now the most international of all drugs, for they may be discovered on one continent, analyzed, investigated, and developed on another, tested on still a third continent, and end up by being used in all quarters of our globe. Never has medicine been more truly historical in its scientific outlook or more universal in its horizons than in the antibiotic field.

HISTORICOPSYCHOLOGICAL BACKGROUND TO THE RESEARCH ON ANTIBIOTICS IN OUR TIME

The historical reasons for the discovery of antibiotic medicine and its extraordinary progress have not hitherto been under consideration. There has never been pure chance in any discovery in the medical world, for all such events have always been tied in some way or other to the cultural atmosphere of each period, which fosters the development of certain types of discovery in preference to others. Medicine is moreover but one aspect of human endeavor, which may also manifest itself in other forms, say, literature, architecture, or music. It is therefore necessary to assess the determining factors in any particular period in the story of civilization if we wish to understand exactly the meaning of medical discoveries during such a period.

A few months from now we shall be commemorating the tercentennial of the death of William Harvey. To appreciate properly Harvey's discovery of the circulation of the blood, which changed the face of medicine after some thirteen centuries of error based on Galen's physiology, it is vital to consider the cultural atmosphere of his age in a Britain and a Europe at the full height of the Renaissance. For without the sudden enthusiasm for *motion* in art, embodied in Michelangelo's work; without the triumph of the new dynamic conception of art as attested by the outburst of *chiaroscuro*, of spiraling columns that ousted the classical Greek and Roman pillars and capitals, and, above all, of baroque work that wrenched the stone of cathedrals and palaces from the mystic ecstasy of Gothic art and turned it into veritable whirlpools—without an awareness of all this, it would be impossible to understand how Harvey came to make that splendid leap from the static anatomy of Vesalius to his *Anatomia Animata* which we now call physiology. And again, how he came to make his discoveries in embryology, which was another form of creating animate anatomy *in time*, just as physiology was its embodiment *in space*. The yearning to find *motion* in all forms of existence that pervaded Harvey's era, the constant mention of blood and the heart, then in vogue, as attested by Shakespeare's plays, provided the philosophic atmosphere for Harvey's discovery that the blood *moves* and that it does so *in a circle*.

In our time, the increasing concentration of the scientific minds on the study of antibiotics may be considered by future historians as the philosophic expression of an age in which every effort—art, physics, science in general—was focused on disintegration, on the reduction of man and his universe to atoms. Perhaps as a reaction against the great philosophic synthesis that ruled in the eighteenth and nineteenth centuries, our own period has been inflamed with the desire to break down and analyze the infinitesimal portions of the human body, of Nature, and of the universe, a desire that has been profoundly reflected in the arts.

For there is undoubtedly an obvious parallel between surrealist painting, which has split into fragments the image of man and his surroundings, nuclear physics, which has broken the universe into atoms, modern poetry, which has disjointed the rhyme and dislocated the strophe, modern architecture, which has replaced substance and solidity in building by a minimum of stone and steel to allow the outer light to enter, thus fusing the outside world with the interior hearth, and modern biochemistry, microbiology, and histopathology, which have ceased contemplating wider problems in combination and instead have focused their attention on the most minute parts of the living being and the tiniest particles of inorganic matter.

But the pendulum of history will inexorably return to its starting point, after having traced another epoch on the clock of Eternity. Before the present century comes to an end, civilization—and of course in its train medicine, which is but one of its many facets—will reach back to the wider conceptions of philosophy and monumental synthesis, to a greater classicism in art and a resumption of the *integral* study of the human being in the psychologic and biologic senses, a tendency that is evident even now. Antibiotics, then, as part of this tendency toward integration, will not be thought of merely as therapeutic agents, but all of the knowledge amassed in their study will be applied to other fields in medicine and even in allied sciences, such as agriculture, and will serve as a key to open new doors to scientific knowledge.

MEDICAL KNOWLEDGE AND MEDICAL COMMUNICATION

We have said that antibiotic medicine already has an impressive endowment of learning and theory, which is ceaselessly being renewed and increased, thanks to the efforts of clinical and laboratory researchers. This poses the problem, ever more urgent and demanding of solution, as to how this tremendous amount of scientific knowledge is to be sorted, coordinated, classified, and brought under effective control.

It took three hundred years of constant labor to compile the *Corpus Hippocraticum*, which comprised the whole of the medical wisdom of the Grecian world and became a scientific instrument for physicians for more than a thousand years. Nowadays, however, the hundreds of thousands of printed pages on antibiotic medicine are but a small portion of modern medical learning; the physician these days must also keep abreast of developments in many other areas of that vast and kaleidoscopic canvas that is our modern medical background of knowledge.

To a certain degree, the body of learning in antibiotic medicine is already overrunning the time and the receptive capacity of the practicing physician. It is vital therefore that we organize this knowledge before it becomes a shapeless, chaotic mass, that we organize it and integrate it into a properly classified and comprehensive code. Let us spend a few moments therefore in considering the problems posed by the mass broadcast of present-day antibiotic knowledge, which is one aspect of the urgent necessity in medicine to solve without delay the problem of *medical communication*.

The goal of medical practice has been the same throughout its whole history: to cure and, if possible, to prevent diseases. Medicine started as—and always will be—a *service* to mankind, the desire of one human being, the physician, to succor another human being, the patient, by helping him to cure or forestall his disease. Medicine, however, was also an *art*, in that it required from the physician what every art demands, namely, a combination of imagination, feeling, skill, and experience in expressing himself artistically, which for the physician would be the satisfactory conclusion of his mission to heal. While medicine remained only a service and an art in the ancient world, medical knowledge was transmitted in the main by word of mouth, and medical teaching was imparted by master to pupil, from generation to generation, until it gradually started to take on a more permanent form when all knowledge was embodied in a *summa* or a *corpus*, such as the Hippocratic Collection, the Treatises of Galen, and the Canon of Avicenna, which were the basic tools of medical learning for more than fifteen centuries.

It was when medicine started to acquire the nature of a science—science requiring the objectivity of the written word as against the emotionality of the spoken word—and when to that was added the invention of the printing press, that the now fearsome problem of medical communication began to rear its head.

The library of a physician practicing in Greece in Pericles' time consisted of a few scant ancient papyri; that of a Roman doctor in the times of Tiberius of the *Corpus Hippocraticum;* that of an Arabian *hakim* practicing in Moorish Granada under the Abbasid caliphs of the Canon of Avicenna and a treatise or so of Galen's; but already in the time of Guy Patin, in seventeenth century Paris, a French doctor's library contained thousands of volumes. These days, the physician desirous of keeping up to date in his profession has to add to the thousands of medical books the thousands of medical magazines and journals now in existence. One can well appreciate that he is faced by a frightening problem of medical communication, which his predecessors in ancient times never knew.

THE DUTY TO COMMUNICATE

Medical communication consists of three factors: the medical information itself, be it printed, speech, or film; the author; and the reader, listener, or spectator.

We therefore recognize that transmittal of professional knowledge from one physician to others has recourse to two means: *visual*—the printed word, photographs or sketches, film or television; and *auditive*—lesson, lecture, radio talk, phonograph record, tape recording, or television.

Here we shall refer mainly to the printed word, the other means of medical communication being merely alternatives. The *word* is essential for the survival not only of science but of man himself, since without words there can be no transmission of thought, and without thought there would be no mankind.

I am not one of those pessimists who say that too much is being said and written in the medical world today. Quite the contrary, I believe that we should talk and write still more, but that we should do it better, and only when we have something positive to say, something that will stimulate, or inform, disclose or confirm some fact or finding that will be of value to other physicians.

It is useless to complain about the excessive number of medical works published every day. The printed word is here to stay, and every day it will increase in quantity.* Instead of mourning the fact that the physician cannot simplify his existence by bringing it down to a single medical text, like the physicians of Plato's Greece, and do without all medical magazines, like the physicians up to 1679 when Nicholas de Blegny, surgeon to Louis XIV and his queen, founded the first medical journal, *Nouvelles Découvertes sur toutes les Parties de la Médicine*, let us accept the state of affairs as it is. Let us be glad that there is such a plethora of material on which to draw, and set our wits to work to devise the best form in which to make proper use of it.

Ethical values in medicine, such as the relationship between doctor and patient, are eternal and immutable. The idea society has regarding the patient may change, as, for instance, from the ancient Babylonian concept of him as a sinner to the primitive Christian concept of him as a potential saint. The basic principles of medicine, however, do not vary. The physician continues to be both an artist and a man of science, for he requires not only science and experience but also intuition and skill, just like any practitioner of an art. Let us not forget the common origin of art and medicine, and that to the ancient Greeks medicine was *techne* (craft) and the physician was as much a craftsman as the sculptor or carpenter, while in Leonardo's Florence painters were members of the Guild of Physicians and Apothecaries, through whose good offices they purchased their pigments.

As a man of science, the physician must communicate his discoveries so that others may benefit from them and that they may remain on record. As an artist, he must also do so if he is to exercise his profession efficiently and with skill. When the doctor imparts something he has learned because he wishes to make a contribution to scientific progress, he is helping medicine *as a science;* when he does it because he wishes to assist others with his empirical knowledge, he is helping medicine *as an art*.

THE TRANSIENT NATURE OF MEDICAL PAPERS

Unfortunately medical documents enjoy but a short life. This is a point worthy of our consideration. A work of art is immortal. The frescoes and murals that thrilled the residents of imperial Pompeii stir our emotions to this day. That "Moses" by Michelangelo in front of which the Doges stood in ecstasy in the church of San Pietro di Vincoli in Rome had the same effect on Sigmund Freud four hundred years later. And while the world lasts, the sculptures of Phidias, the canvases of El Greco, the Taj Mahal, the massive granite of the Escorial, and the exquisite chased chalices of Benvenuto Cellini will continue to fill the soul of man with wonder.

A medical paper, however, has a very short life. Apart from the Hippocratic Collection, the Treatises of Galen, and the Canon of Avicenna, that sacred trilogy which universally held first place for more than fifteen centuries, we need take only one glance through Boerhaave's "Pathology," which was a lamp of learning for the whole of Europe during the seventeenth century, Kraepelin's "Psychiatry" in

* There are around 10,000 medical journals in the world, and more than 3000 books on medicine are published every year.

the last century, or even the later "Endocrinology" by Falta, to perceive that apart from their historical value none of them has withstood the passage of time and medical progress.

Furthermore, the span of life of a medical document becomes shorter every passing day as we continue our advances in medical science. Osler's descriptions of pneumonia, typhoid and other infectious diseases have succumbed to the impact of antibiotics as far as their natural history is concerned. The natural history and biologic cycles of disease will continue to change as new drugs are discovered.

To cite a current example, the picture of mental diseases will vary as much in the next ten years with the use of ataraxics as that of infections has varied during the last fifteen years with the use of antibiotics. All this will only aggravate the problem of medical communication by demanding that each and every record be constantly rectified and brought up to date as further progress is made. Hence the pressing need to increase the flow and rhythm of medical communication.

In another paper* I discussed some of the problems of medical communication as follows:

> The greatest problem of modern medicine is that of communication. Communication not only between the physician and the sick person, so indispensable particularly in psychiatry, but also between the investigator and his problems, the clinician and the patient, and the educator and his pupils. Especially vital is the need to communicate scientific finding, clinical data, medical discoveries, or the great-in-its-humbleness daily medical experience to the professional who needs to know all this in order to fulfill better his ministry. Despite the progress in radio, films, and television, books and journals are still the best vehicles of medical communication.
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> "There are only three pleasures in life pure and lasting and all derived from inanimate things—books, pictures and the face of nature," said William Hazlitt. These three supreme components are represented in a medical journal by the word, the image, and the phenomena of human nature either when it is normal or when it is undergoing that painful "mode of life" that we call disease.
>
> "In the beginning was the Word . . ." and in the beginning as well as in the end the written word and the image were and will be the most faithful messenger of medical thought, a flowing tunic clothing thought without disguising its true form.
>
> In the world of medicine, events occur in the hospital ward, in the physician's office, or in the research laboratory. After these phenomena have been recorded by the eyes and ears of the observers or by the camera's magic pupil, they are transmuted into words and images that later, on the printing presses, are converted through electrical impulses and mechanical vibrations into articles and photographs which, lastly, are integrated into the pages of a medical journal. As happens in every biologic cycle, this process is a continuing one. Readers of medical journals transmute in their minds the words and images into ideas and concepts that will help them in carrying on their research, clinical practice, or medical teaching, thus creating new links in this endless chain of development.
>
> Medical journals integrate the three categories established by Osler—"creators, transmuter and transmitter," since they create a climate of opinion around scientific problems, transmute phenomena and events into ideas and concepts, and transmit to their readers not only the golden stream of classical medical wisdom, but also that other "small" daily clinical wisdom which, like a fine rain of gold dust, is daily precipitated upon the mind of the general practitioner.

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* Martí-Ibañez, F.: Words and images in medical communication, Internat. Rec. Med. *169*:32, 1956.

What can be done to solve the problems of medical communication in the case we are concerned with—in the field of antibiotic medicine?

THE BASIC PROBLEMS OF MEDICAL COMMUNICATION

First of all, what are the basic problems of medical communication? In my opinion there are four: (1) To ensure that every valuable medical or scientific discovery, theoretical or practical, shall be published, and as soon as possible, cutting down to the minimum the period elapsing between the moment of discovery and that of its communication to the rest of the profession; (2) to ensure a world-wide distribution for every valuable medical paper, overcoming geographic and language barriers; (3) to organize, coordinate, and integrate all antibiotic knowledge into an efficient and always up-to-the-minute source of antibiotic data; and (4) to guarantee maximum speed in incorporating into medical practice any reported scientific advance by translating it into adequate practical measures.

Such a program of ideal objectives in the field of medical communication would help to bring about a revolution in service to the physician and consequently to the sick, who are dependent upon how much and how soon the physician learns of the newest advances in medicine.

Medicine is becoming more technical and more specialized every day. This the general practitioner feels more than anyone else, for every day it becomes more difficult for him to obtain and master such knowledge and integrate into his own practice the most important advances in each particular specialty. While specialization existed in previous historical periods, medical learning in those times, however, was not so extensive that it created problems for the general practitioner, as it occurs today.

What, then, can we do to solve these problems?

First, we should recognize one principle that is often utterly disregarded: the most important thing in medicine is not to report one's findings; the most important thing in medicine is *to communicate, to propagate one's findings.*

No one, as far as I know, has ever stressed this most basic principle. There is a world of difference between "reporting" and "communicating." The Spaniard Servetus "reported" his discovery of pulmonary circulation in his treatise "Christianismi Restitutio," published in 1553; but it was not until many years later that his discovery was fully "communicated" and accepted by the medical world. The same thing occurred with the discovery of percussion by Auenbrugger, vaccination by Jenner, x-rays by Roentgen and antiseptic surgery by Lister. Two Austrian investigators, Meyer and Nally, reported the synthesis of isoniazid in the journal, *Monatshefte für Chemie und verwandte Teile anderer Wissenschaften;* but it was not until 1952 that it was made known to the medical world and tested in pulmonary tuberculosis. Fleming dutifully reported his discovery of penicillin in 1928; but it was not until 1940 that, thanks to Florey and Chain, his discovery was placed at the service of mankind.

History abounds with cases of important discoveries buried among the dusty pages of some unknown publication that not until many years later were wrested

from oblivion, studied, and applied. Today this happens far too often, with the result that several scientists may be duplicating one another's work, or that one man may devote his life to repeating work already carried out by someone else many years before, or that thousands of doctors the world over may be deprived of the benefit of a multitude of scientific advances that would make their work easier and more efficient. *Much is reported but not enough is communicated.* Reports are minute editorial pebbles cast in the waters of the wide lake of medical literature, whose expanding ripples die out before they reach those on the distant banks who could put them to proper use.

ON THE ART OF CLEAR WRITING

What can be done to remedy the state of affairs in which much is reported but not enough is communicated?

Above all, the physician must communicate everything that may be of theoretical or practical value to others. It is not enough that one knows something, one must tell it to everyone else. The distinction is the same as that existing between the commonplace instructor who imparts but a fraction of his knowledge and the true teacher who teaches everything he knows.

The mere fact of expressing in words a discovery of any kind is already a means to making it permanent, to understanding it and improving it further. The written word is the most dynamic force on earth. Harvey's winged words started the medical revolution that led to present-day physiology; Fleming's simple description of his discovery initiated the antibiotic revolution; Freud's bold words changed the whole field of medical anthropology and psychopathology. Too many physicians and research workers are afraid to reveal their findings, because, for example, they may be used on one single case or on a small group of cases, or because the data obtained are negative.

Referring only to these two reasons for silence, I would stress that the single case in medicine, just like the single and isolated earthquake or flood in geology, may be of the greatest instructional value, while a negative result may well be the key that opens the door to a whole treasure-house of positive results. It is therefore imperative to write and communicate everything you know, distilling into written words the unique and valuable experience of every individual.

The writing and publishing of one's knowledge may be stimulated by closer contact between the author and the editors of medical journals, which are the most universal means of medical communication. The mission of the public censor is to say, "You can't do that"; but the editor's job is to say, "That's the way to do it!" The editor works constantly in the field of medical communication, and his advice, inspiration, and guidance may be invaluable to many physicians and research workers less versed in this art.

I believe that no fixed rules can be laid down for the writing of good medical literature. This may smack a little of heresy, coming as it does from one who has devoted a good part of his life to medical communication. Nevertheless, I repeat, I do not believe in fixed rules for writing good medical literature. Suppose there

had been applied to the writings of Osler, Oliver Wendell Holmes, Cajal, Mackenzie, and Freud those strict rules that some people now recommend—the methodically clipped phrase, short, simple words, avoidance of all rare, rich, or colorful expressions—then medical literature would have been deprived of some of its greatest masterworks. I do believe, however, that there are certain principles of good writing whether it be on medicine, art, mathematics, carpentry, or travel. The principles of "lucidity, simplicity, and euphony" recommended to young writers by Somerset Maugham in *The Summing Up* are indeed the best rules one can think of for the creation of good medical literature also. Literature is an invaluable aid to medicine. Did not Thomas Sydenham advise Blackmore to learn medicine by reading *Don Quixote*?

SYMBOLS, METAPHORS, AND THE SEMANTIC PROBLEM

We must withal improve our art of communication by learning to write more and better, so as to arrive at some common denominator in medicine that may smooth the path for physicians and investigators throughout the world to understand one another better. This brings us to the point of the problem of semantics in medical communication.

Man's greatest invention has been that of signs and symbols, i.e., written signs or sounds to represent objects and ideas. From the moment of birth man has to face all sorts of problems and situations. To solve these, man uses signs and symbols as a means of recalling past problems, cataloguing his present ones, and anticipating those of the future. In turn, he applies to such symbols the principles and rules derived from what we call science, grammar, logic, or physics.

Symbols, however, are not always accurate or trustworthy. Every human being has his own inner picture of the external world, a picture that differs with every person, since it is formed exclusively by what each one personally knows or imagines about things, people, and places in the outer world. In his turn, each person reflects and projects upon the world and upon all other creatures his inner picture of the world, partial and inexact though it perforce always is. It is as though the world were reflected in millions of mirrors—the individual minds of man—every one of them with a different radius of curvature; all reflections therefore are different.

If we bear this in mind, the problem of human communication becomes simplified when everyone recognizes that his picture of the world and of things is not the only one, that it is no more accurate than anybody else's, and, above all, that *it is only an image* and not the external objective reality. If we make a thousand people look at a painting, or if we read them a poem, or show them a film, or play a sonata for them, each person will have an impression different from that of the others. The mission of science is necessarily to restore the true value and meaning of our symbols, remembering all the time that they are only metaphors for reality and not immutable dogma. That is the way science attains its greatest dignity and efficiency, for, while dogma has been the historic ballast to theology, metaphor has been the flying wing of science.

The secret of progress in medical communication therefore depends on realizing

that symbols shall represent not individual images, not the engrams within each human mind, but objects and facts that are objective expressions of the interrelationships between things, creatures, and realities in the outside world. Precision and objectiveness in scientific language and the proper use of symbols as representations of external correlations are indispensable conditions for a satisfactory communication among men in the field of medical science.

A NEW CONCEPT OF MEDICAL JOURNALISM

Where must we publish? Wherever we can, but we should try to reach those journals that have a receptive intellectual audience.

I firmly believe in the social and scientific mission of the medical publications distributed free to physicians, so much so that I publish a journal that is sent free to a great number of physicians; yet its ethical and professional character has not been jeopardized. In this manner, I feel, we are anticipating the future. For the physician of tomorrow will have *free* access to many publications for which he at present has to pay and to which he is often unable to subscribe.

The mission of a medical publication is *to communicate*, and if the only way to fulfill this mission is to send it gratis to the profession, then by all means let us take this bold yet constructive step forward in the art of medical communication. The proof that such a step is only anticipating by a few years the medical world of tomorrow, when physicians will receive free most of the professional publications to which they now have to subscribe, is that the great pharmaceutical companies who have been revolutionary pioneers in the field of antibiotic medicine have already recognized this need. Their assistance to scientific publications, by means of their advertisements, is helping to solve that vital problem of medical communication: to bring out at the *earliest* possible date, to as *many* people as possible, the *greatest* possible number of the *best* possible medical works.

A medical publication should not be an ivory tower. It should be an open forum accessible to all physicians and research workers where they may speak freely to all their colleagues. In theory as in practice, that is what I think, and that is the way I have directed the course of our modest contribution to the solution of the problem of medical communication in the field of antibiotics.

CHAIRS IN ANTIBIOTIC MEDICINE AND THE INTERNATIONAL ANTIBIOTIC INSTITUTE

But what can one or even several publications do? A great deal more must be done and that on an international scale. Herman T. Biggs once made a statement that became the motto of the New York State Public Health Department: "*Public health is purchaseable; within natural limitations any community can determine its own death rate.*" So also might we say that medical communication can be financed, and within certain limits each medical community can determine the degree of knowledge its members may attain.

Who better than the pharmaceutical industry could organize, coordinate, and integrate on an international scale the vast and increasing knowledge on antibiotics?

From this platform every year for the past three I have launched a call, which I now repeat, to the pharmaceutical industry to establish Chairs in Antibiotic Medicine in various countries of the world and to set up an International Institute of Antibiotics dedicated exclusively to organizing knowledge in this field, a center to act as a universal brain for receiving, classifying, synthesizing, and making available all printed material on antibiotics. Such an international center, by means of its publications, chairs, traveling professors, iconographies, and museums, could solve the problem of world-wide communication of antibiotic knowledge, which in turn would ensure increasing progress in antibiotic medicine.

This is no castle in Spain, no Utopian vision; it is an all-compelling necessity which will aid both the abstract science and the practical art of medicine. Such an institution might very well help the modern physician to become what more than two thousand years ago that magnificent Athenian, Plato, demanded: the medical statesman—the *Asklepios politikos*.

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MEDICAL INSTRUMENTS SECTION*

Evaluation of the Hardy-Wolff-Goodell Pain Threshold Apparatus and Technique: Review of the Literature

Austin H. Kutscher, D.D.S.,† and Helene W. Kutscher, B.A.

NEW YORK, N. Y.

Since first described in 1940,[71] the Hardy-Wolff-Goodell pain threshold apparatus and technique have been used extensively in the study of pain, the pain threshold, and the pain threshold-raising action of analgesics. Many favorable and/or unfavorable comments have been directed at the apparatus and technique for various reasons. This study was, at its inception, a personal attempt to clarify certain issues that arose during studies in our laboratory.[24–28] However, so many of those with whom we ultimately corresponded expressed interest in our over-all findings that we decided to perform the exhaustive investigation that follows: a review of the literature (including bibliography) concerning the applications and findings with regard to the Hardy-Wolff-Goodell apparatus and technique; an evaluation of the reliability, usefulness, and accuracy of the apparatus and the technique as evidenced by the findings, difficulties, and comments embodied in published reports of the investigators who had previously worked with the technique and apparatus and contained in personal replies to questionnaires mailed to many of them; and the variation in the pain threshold in human subjects as described by these investigators when using the Hardy-Wolff-Goodell (henceforth abbreviated as HWG) pain threshold (henceforth abbreviated as p.t.) apparatus.

In the HWG technique, p.t.'s are determined by focusing the radiant heat of a 500 watt projection bulb through an electrically timed solenoid shutter for three seconds onto the skin, which has been blackened with India ink to assure complete and uniform absorption of radiation. The pain threshold, measured in millicalories per second per square centimeter of exposed skin, is considered the amount of heat required to provoke a sensation of heat, finally "rising" or "swelling" to a distinct stab or prick of pain at the end of the three second exposure.

At least one study of virtually every investigator for whom it was possible to obtain a paper was included. An attempt was also made by questionnaire to obtain

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* The Medical Instruments Section will be featured in this journal during 1957. Outstanding authors have contributed articles to this series that will depict a panorama of the role of scientific instruments in clinical medicine.

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the personal opinions of the authors of the various publications dealing with the HWG technique. Because of space limitations, our findings are not reported in great detail, it being our intention, rather, that they should serve principally as a guide to further study.

APPLICATIONS OF TECHNIQUE

The various studies of the HWG technique and apparatus have dealt with: the original technique;[71–76] pain sensitivity;[9] adaptations of the HWG apparatus or technique;[16, 57] skin temperature effects;[9, 58, 67, 68, 70, 75] dol scale of pain intensity;[73, 74] hyperalgesia;[8, 43, 66, 72] pain physiology;[4, 5, 9, 20, 26, 27, 33, 60, 63, 65, 80, 81, 87] reflex responses;[10] hypoxia and hypercapnia;[55] effect of analgesics (including opiates) on;[1–3, 5–7, 10–19, 23–25, 27–32, 34, 37–42, 47–54, 56, 59, 64, 79, 82, 84–86] analysis of algesimetric methods;[39, 62] pain experience during disease;[21, 26, 27] pain threshold in disease;[22, 33, 36, 43–45] evaluation of the p.t.;[33, 35, 46, 61, 76] topical anesthetics, effect on p.t.;[69] attitude and suggestion, effect on p.t.;[82] and statistical treatment of data.[90]

REPRESENTATIVE FINDINGS

Comparatively little of Hardy-Wolff-Goodell's work has been included in this report since it was not our primary purpose to report their evaluation of their own technique and since this is readily available from either their originally published works[20, 21, 63–77] or their book, *Pain Sensations and Reactions*.[78]

The findings obtained in a large representative group of general studies dealing with the HWG technique (but excluding, in general, the work of Hardy-Wolff-Goodell) are summarized herewith.

Chapman and Jones, with untrained subjects, noted that pain sensitivity decreased with age. A group of Negroes had a lower p.t. than a comparable group of north Europeans. Mediterranean races' p.t. corresponded closely to that of the Negro. Mental fatigue and nervous tensions produced significant changes in p.t. Pain perception was felt probably to represent a purely sensory phenomenon and pain reaction to represent a psychologic phenomenon that may assume clinical importance. The magnitude of individual threshold variations in pain perception and reaction in normal patients was felt to be of real clinical significance.[89]

However, Schumacher et al studied the p.t. in 150 persons of different ages and of both sexes and concluded that the p.t. could not be correlated with the subject's estimates of his sensitiveness to pain; was relatively stable and uniform in man; was uniform throughout the 24 hour day and not affected by feelings of lethargy, tension, and overirritability, nor by lack of sleep for a 24 hour period. Individual reactions, they concluded, to pain were not the result of individual variations in p.t.[46]

Kunkle and Chapman found that the p.t. mean for a group of 200 normal individuals was 0.305 mcal. (millicalories), a significantly different average normal than that reported by Hardy-Wolff-Goodell. At an intensity of stimulus of approximately 600 mcal., one subject, a young man almost insensitive to pain, noted only moderate warmth and, in some of the tests, a slight pricking sensation. Yet his skin became blistered. Exposure of normal individuals to a stimulus of this intensity of course produces severe pain.[33]

Schilling and Musser noted that 22 patients with menopausal syndrome had average pain reaction thresholds significantly lower than a control group of 44 "non-neurotic" adult female patients. Pain perception and pain reaction thresholds of menopausal women closely resembled those of psychoneurotic persons. When the reaction level was so low as to be identical with the perception level, the subject was most likely suffering from a definite emotional disorder. In the group of 22 "menopause" patients, 5 showed a fusion of perception and reaction thresholds as opposed to none of the 44 "non-neurotic" patients.[44]

Bigelow et al investigated the nature and significance of pricking and burning pain. The "burning" p.t. was found to be lower than the "pricking" p.t. During the phase of incomplete analgesia following infiltration of procaine hydrochloride, 1 per cent, into the skin or about a peripheral nerve, "pricking" pain was perceived, whereas "burning" pain was abolished. It was concluded that "burning" pain was conveyed chiefly by unmyelinated fibers and "pricking" pain by myelinated fibers.[8]

Hardy et al reported that regardless of the duration of the heat stimulus, pain sensation and reflexes were elicited at about the same temperature, 45 C. Pain and reflex responses evoked by thermal noxious stimulation of the skin were suggested as depending only on the level of skin temperature and not on the duration of elevated skin temperature. The same process (thermal inactivation of tissue proteins, probably of the pain fiber endings) was thought to underlie pain elicitation and reflex response. Thermal noxious stimulation was characterized by the rate of certain reactions (probably involving protein inactivation) rather than by the amount of tissue damage caused. P.t. and reflex response to noxious stimulation by heating was considered probably determined by the lowest rate of inactivation of tissue proteins that will cause tissue damage if the thermal stimulation is sufficiently prolonged.[20]

Wertheimer and Ward provided further confirmation that "the skin in the areas tested must be raised to a temperature of 44.9° C to be noxiously stimulated, regardless of the initial level of skin temperature."[55]

Birren et al described a correlation of 0.91 between two successive p.t. determinations on 50 subjects; the standard error of measurement was 12.5 mcal. Correlation between the mean of two determinations on days 1 and 2 was 0.86 for the same 50 subjects. With constant stimulus duration (three seconds), significant variation in p.t. was produced by varying the skin temperature at 85, 90, and 95 F. At a skin temperature of 90 F., a significant relationship was found between threshold and stimulus duration. For accurate assay of analgesic efficacy, it was determined that the skin temperature should be held constant to exclude influence by body temperature and/or cutaneous blood flow.[9]

Wertheimer, instead of varying the millicalories per second delivered, as in the HWG technique, held the heat stimulus constant at 275 mcal. and measured the p.t. in terms of the length of time a constant stimulus had to be applied before the subject reported pain. He suggested the following advantages: one trial yields a quantitative determination of the p.t.; resultant hyperalgesia is of no importance; p.t. measurement takes only a few seconds; since only one stimulus-setting is required, calibration of the apparatus is less time-consuming; any setting that does not produce

pain immediately, and is not so weak as never to produce pain, may be used; the measurements obtained by the single trial technique may be translated into the usual units.[57]

Hazouri and Mueller studied the p.t. in 100 paraplegics and quadriplegics and found that these patients followed the pattern of nonparaplegics. With intractable pain, 3 patients showed a distinct increase in the p.t. and an even more marked increase in the reaction threshold. Lateral spinothalamic tractotomy resulted in complete relief from pain and return of the p.t. and reaction thresholds to normal range.[22]

Potelunas et al studied the unaffected and pathologic skin of dermatologic patients with pruritic and nonpruritic lesions. Tissue damage resulting from dermatoses was felt to be an infrequent cause for altered p.t.; lowered p.t. in the area of skin lesions was thought to be the result of a particular type of tissue injury that is capable of maintaining a poorly understood state of hyperexcitability in the superficial pain endings. No correlation between itching and altered p.t.'s was found; itching and superficial pain were not felt to be interdependent sensory entities but result instead from different causes. Changes in sensitivity to painful stimuli in areas of skin damage were thought generally to parallel observed changes in p.t.[43]

Hardy and Javert measured the pain intensity in childbirth; pain intensity was observed to change with the progress of labor as follows: first stage—from first to fourth quarters—threshold to 10 dols; second stage—10 to 10½ dols (ceiling pain); fourth stage—3 to 5 dols to near threshold value in about two hours after delivery. The p.t. remained within normal range for all patients who had received no analgesia or anesthesia.[21]

Andrews has made simultaneous measurements of p.t. and skin resistance that should furnish a means for differentiating between autonomic effects and those involving higher centers and also for differentiating various aspects of drug action.[4]

ANALGESIC TESTING

The drugs that have been investigated using the HWG technique to determine their analgesic effect (in terms of the numerical increase or decrease in millicalories—or the percentage increase or decrease in the p.t.—after their administration) are as follows: acetanilide,[25] acetylsalicylic acid,[10, 22, 53] ACTH,[56] alpha-iso-morphine,[3] amphetamine,[40, 41] d-amphetamine,[18, 42] Antistine,[27] apomorphine,[28] atropine,[13] codeine,[2, 6, 50] codeine phosphate,[52] codeine sulfate,[31] cortisone,[56] Demerol,[6, 18, 26, 28, 48] dihydrodesoxy-morphine,[3] dihydrohydroxy-codeine,[3] Dilaudid,[3, 52] Dolophine,[48] epinephrine,[16] glycinanilide,[25] heroin,[3, 26, 28] 3-hydroxy-N-methylmorphine-hydrobromide,[59] meperidine,[18, 40, 41] methadone,[11–13, 15, 18, 24] methadone (HCl),[11, 49] methyldihydro-morphinone,[3] monoacetylmorphine (HCl),[29, 50] morphine,[2, 3, 6, 13, 15, 18, 26, 28, 59] morphine sulfate,[1, 13, 19, 25, 29, 32, 50, 52] neostigmine,[13, 50, 52] neostigmine methylsulfate,[52] nitroglycerine,[18] nitrous oxide,[14, 40, 42, 53] oestrone,[1] oxygen,[14, 42] Pantopon,[52] procaine hydrochloride,[7, 26, 30] Prostigmine,[2] Pyribenzamine,[27] saline,[28] scopolamine,[13, 26, 28] sodium chloride,[15] sodium phenobarbital,[32] sodium salicylate,[10] Subdamine,[24] sucrose,[32] Teropterin,[51] d-tubocurare chloride,[1] xenon.[14]

TABLE I

Relative Potencies of Analgesic Agents When Compared with the Hardy-Wolff-Goodell Technique

These agents were more effective in raising p.t.	*<than>*	*these agents*
morphine[8]		methyldihydro-morphinone
Demerol[6]		codeine
methadone[11]		morphine sulfate
methadone[12]		morphine
morphine[13]		morphine and atropine or scopolamine
morphine[13]		methadone and atropine or scopolamine
morphine sulfate[29]		monoacetylmorphine hydrochloride
Bromoaspirin[31]		Aspirin
N_2O (33 per cent with O_2) and meperidine with amphetamine[40]		meperidine
N_2O (33 per cent with O_2) and meperidine with amphetamine[40]		N_2O (33 per cent with O_2)
meperidine and amphetamine[42]		meperidine
Dolophine[48]		morphine
methadon[49]		methadon d
neostigmine and morphine[50]		morphine
neostigmine and Dilaudid[50]		Dilaudid
neostigmine and Pantopon[50]		Pantopon
neostigmine and codeine[50]		codeine
neostigmine and Dilaudid[53]		Dilaudid
Nu-2206[59]		morphine

These agents were equally effective in raising the p.t.	*<as>*	*these agents*
morphine-Prostigmine[9]		morphine
Demerol[6]		morphine
procaine hydrochloride[7]		acetylsalicylic acid
procaine[7]		physiologic saline
sodium salicylate[10]		placebo
monoacetyl morphine[59]		morphine
acetylsalicylic acid[53]		placebo

The following agents were reported as raising the p.t. to some degree in human beings: acetanilide (animals),[25] acetylsalicylic acid,[7] amphetamine,[42] codeine,[3] Demerol,[6] glycinanilide (animals),[25] heroin,[3] meperidine,[13, 40, 42] methadone,[11, 13, 24] morphine,[13] morphine sulfate (variable),[32] in animals,[25] neostigmine,[52] 30 per cent nitrous oxide,[55] nitrous oxide 5 per cent with 7.5 per cent carbon dioxide,[55] nitrous oxide with oxygen,[14, 25, 40] Nu-1196,[19] Nu-1779,[19] physiologic saline,[7] procaine hydrochloride,[7] Teropterin,[51] and xenon.[14]

The following agents were reported as ineffective in raising the p.t. in human beings: acetylsalicylic acid,[32, 53] ACTH,[56] Antistine,[37] atropine,[13] cortisone,[56] neostigmine,[13] oxygen,[55] phenobarbital,[32] placebo,[10] procaine,[30] Pyribenzamine,[37] scopolamine,[13] sodium salicylate,[10] sucrose,[32] and Subdamine.[34]

Table I suggests relative potencies of analgesic agents when compared with the HWG technique.

DISCUSSION

Factors to Be Considered as Affecting Results. The particular usefulness of the HWG technique lies in that, however the end point is described, it is theoretically possible to duplicate the p.t. on subsequent trials and after the administration of drugs. The radiant heat method of pain measurement offers the advantage of an easily controlled and measured stimulus. Some subjects, whether or not they have ever before participated in p.t. determination work, give consistent results. Others do not. Once established for an individual, his normal threshold is apparently reasonably constant.

In addition to the considerations noted previously with regard to testing procedures and the application of the technique, as described by Hardy-Wolff-Goodell, the following points also seem worthy of note.

Skin heat dissipation determinations indicated that at least two minutes of rest must elapse between successive stimuli. Care must be exercised not to inflict burns when high pain intensities are measured; measurements cannot be made in the face of distraction or lack of cooperation. A "learning effect" may affect p.t. determinations consistently, although in small amounts, as testing continues. Unless a radiometer is available for periodic recalibration, the instrument employed is useful only in short term experiments in which the absolute value of the p.t. is not essential.

Different areas of skin must be stimulated in each exposure; as few stimuli as possible should be given to locate the threshold accurately. An average of four stimuli may be sufficient to determine the p.t. within ± 10 mcal. Measurements of the pain sensitivity of an individual in the light of current knowledge may require about an hour, allowing the recommended minimum of two minutes between stimuli, two determinations of p.t., and skin temperature regulation.

It is probable that p.t. data cannot be duplicated in patients who have experienced repeated painful stimuli over long periods of time or who are otherwise very ill. The extent of possible cooperation of patients when in severe pain remains in doubt, and in many such patients, basal conditions are actually unobtainable because of various systemic distress factors. It is now considered probable that skin temperature readings are reliable only on the forehead since the hand may show a considerable degree of spontaneous temperature and other variation. It is interesting to note that almost no emphasis has been placed in the reports reviewed on the training of the observer-tester, an item of utmost importance, the further study of which is *still* indicated. Tests employing the HWG technique on untrained subjects give relatively less reliable results.

The lack of agreement between some reports remains unexplained. Discrepancies may be due to differences in the quality of the sensation taken as the p.t. by various laboratories. One team reported, however, that inconsistencies were apparent not only when one of them conducted the test but also when a physician with years of experience with the technique tested the subjects, even though the apparatus was accurately calibrated and the subjects were intelligent, cooperative college men who had been drilled in the technique before they started. It seemed to this group truly useless to look for subtleties in a method when gross differences could not be made evident.[15]

Kuhn and Bromiley suggest that the discrepancies between their findings and those previously reported by others are due to the use of inadequate methods of p.t. determination with the HWG apparatus, an instrument that nevertheless appears to be ideally suited for such studies.[82]

Epidermal thickness apparently plays a relatively minor role since, although variations in epidermal thickness were ±8 per cent, p.t.'s varied as much as 30 per cent in one group of subjects studied.[89]

Use in Evaluating Analgesics. The HWG technique has also contributed to our knowledge of analgesics. It is imperative that in any study of the analgesic potency of drugs the factor of suggestion be taken into account and that controlled studies be made by use of placebos and double-blind techniques (neither experimenter nor subject knowing that placebo is being used). Crossover of treatments should be carried out, and doses should be below those that produce any side reactions (which would tend to invalidate the placebo treatment). Apprehensive persons might actually show a reduced p.t. The effects of analgesic agents on the p.t. should not be expected to be identical in each individual tested but rather of the same order and magnitude.

However, the p.t.–raising action is only one, perhaps relatively unimportant, part of the process of pain relief. Application of the HWG technique in testing analgesic agents remains an issue clouded with the problem of defining what is an analgesic. Analgesics may not, in some cases, interfere with the perception of pain. Comparatively large doses of morphine may be required to obtain measurable p.t. increases.[3] With the HWG technique, a numerical p.t.–raising effect of an analgesic agent of less than 7 mcal. (even when apparently statistically significant) is most difficult to determine or interpret clinically and is of slight clinical importance. Studies suggest that the relief of pain by opiates involves at least two mechanisms—an increase in p.t. and a reduction in the reaction to a recognized pain. With morphine, the reduction in the alarm reaction has even been described as the more important factor.[4] Mild analgesia obtained from salicylates is probably not a uniform phenomenon when measured by the HWG procedure on relatively inexperienced and perhaps even experienced subjects. Hence, HWG results may have no relevance to the analgesic action of salicylate. It is not implausible to conclude that the HWG technique is mainly useful in testing analgesic agents of higher activity and is probably especially useful as a preliminary screening method to approximate relative potency of new analgesics.

It was not unusual for authors to report that although subjects were not informed of the identities of drugs received, after some experience they were able to identify each compound or combination of drugs by side effects. It was concluded by one group of investigators that "it is unlikely that sophisticated subjects can be deceived" by control measures used by Hardy-Wolff-Goodell in their morphine sulfate experiments.[30] In studying analgesics, oral doses produced decided variations in both intensity and duration in different cases, perhaps due in part to different rates of absorption.

With regard to analgesic testing, it is probable that, over-all, the HWG method should be limited to screening analgesics and that the ultimate test of the efficacy

of the agent should be permitted to depend on its obtunding of pain. It is not to be expected, therefore, that the dolorimeter will replace careful clinical observations of the effects of an analgesic but can be used to supplement and orient the clinical investigator.

Difficulties Encountered. As opposed to the relatively favorable findings in our review of the literature, the following discussion represents the difficulties encountered by other investigators. We have, in the main, let the investigators concerned "speak for themselves" through the medium of relatively unedited, abbreviated excerpts from their personal communications or published reports.

A point worth re-emphasizing is that when a subject is "suggestible," inattentive, or emotionally disturbed, erratic results may be anticipated. Bigelow—personal communication.

Some thresholds were higher after the injection of isotonic sodium chloride solution; some were lower after the administration of morphine; and these discrepancies were common. We were "unable to distinguish between 15 mg. of morphine and a placebo (one cc. normal saline)." Inspection of the data on p.t. determined by the HWG technique revealed such gross inconsistency that a detailed statistical analysis was not justified. (Comment by Beecher: These comments refer to work in man, not in animals.) Denton and Beecher.[15]

"It seems to us reasonable to separate pain on the basis of its origins and significance to the subject; that is, experimental or pathological."[86]

"It [the HWG technique] did not work in our hands. Admittedly, this might or might not be relevant. We did not rest on our own experience. We enlisted the help of a responsible investigator who had worked happily with the method for years and had published a number of articles based upon it. When he repeatedly failed to distinguish between a large dose of morphine and a placebo (as long as he was in ignorance of what had been used), there did not seem to us to be any point in looking for subtleties with the method—as for example, trying to distinguish between two analgesic agents. Nor did we leave matters here; we went to a number of investigators in the field of pharmacology and physiology, men who are well known for their painstaking skill in experimentation and sound critical judgment. They all reported that their experience had been exactly like ours with the HWG method." Beecher.[88]

"The analgesic drugs produce a number of subjective responses which may or may not be related to pain relief-euphoria, for example, 'giddiness,' and so on. In other words, highly experienced subjects who know in general that they are involved in studies on analgesics are certainly not unaware when a narcotic is used and when a placebo is used. They know all too well what responses are expected." Beecher.[88]

It is now fairly well recognized by all in the field that there is no correlation between clinical analgesia and the HWG technique. This method merely reflects insignificant components of analgesic action in man. Unfortunately, too much emphasis has been placed on its accuracy for the introduction of analgesics. Although it reflects the action of the more potent ones, the mild or moderately active analgesics may have no effect in elevating the p.t. Furthermore, an occasional subject,

trained or otherwise, may have a reverse response to a potent analgesic rather than an elevation of p.t. This depression is indicative of stimulation. Batterman—personal communication.

Line voltage drop was a possible source of error but of smaller magnitude than physiologic errors involved. Chapman and Jones.[89]

On the basis of their efforts it is fair to say "that Wolff et al have yet to publish quantitatively acceptable data on human p.t. as determined by means of the HWG p.t. apparatus despite the fact that this equipment appears to be ideally suited for such studies. The differences between the data reported here and those published by HWG and their co-workers may be largely attributed to differences in the method of determination of p.t.s. HWG have devoted relatively little space to a description of the experimental testing procedure they utilized. The authors are unable to find any statement in the numerous articles HWG have published which might indicate what threshold HWG were establishing." Kuhn and Bromiley.[22]

Whatever results may indicate, they certainly show that the HWG procedure cannot be used as a method for studying the relative analgesic potency of various drugs in man. The work was finally abandoned without publication. Isbell—communication.

All degrees of training were represented by various authors, ranging from minimal familiarization with the apparatus and technique to extensive training such as that employed by Hardy-Wolff-Goodell (using themselves) and Javert. A frequent finding in the reports studied was the absence of explanation as to the thoroughness of training of the test subjects. The differences in the training of the various subjects in the studies could well have caused many of the discrepancies in the findings reported, commented on, and disparaged by other investigators included in this report.

It has been suggested, however, that the problem of trained versus untrained subjects is a pseudoproblem. Furthermore, the results may possibly be greatly influenced by the operator also. A sympathetic operator may perhaps obtain more elevations than an unsympathetic operation. Isbell has suggested that the results are better when the operator knows the type and dosage of the drug administered. Further study of the role of the operator in the HWG technique is definitely indicated.

Over-all Evaluation. A summary of the evaluation of the HWG apparatus and technique by as many investigators as possible who have had the opportunity to work with the instrument, as described in personal communications, returned questionnaires, and published works, suggests the following: Papers describing the technique as excellent 6, satisfactory 47, poor 1; questionnaires or personal communications describing the technique as excellent 3, satisfactory 11, poor 3; papers describing the apparatus as excellent 3, satisfactory 52, poor 1; questionnaires or personal communications describing the apparatus as excellent 5, satisfactory 12, poor 1.

When specific statement of the relative satisfactoriness of the technique was not made in a paper, it was assumed that the technique was found, in general, to be satisfactory. This feeling is based, in principle, on the observation that investigators are not likely to use a technique with which they are not satisfied without specific comment to that effect. It should be noted, however, that some authors

may be hesitant to criticize or evaluate critically a technique on which their paper was based. The extent to which this latter factor should be considered cannot be readily ascertained. Over-all, the preponderant opinion of authors derived from this review of the literature was favorable with regard to both the technique and the apparatus in terms of studies dealing with the p.t. and pain physiology, but considerably less so with regard to analgesic testing.

Pain Threshold in Man. The range of the p.t. and its constancy as determined by the reports and communications of the various investigators were reviewed. One of the reasons for the paucity of data on the range of p.t. in man as determined by this technique probably stems, unfortunately, from the fact that p.t. changes have usually been reported only as percentage changes rather than in terms of the actual changes in the number of millicalories, which would have permitted examination of base line thresholds.

The results obtained with the HWG apparatus and technique in the study of the range of the p.t. in man and the opinions derived from these studies by the many investigators, however, vary significantly but, it should be emphasized, during perhaps varying applications of the technique.

Although Hardy-Wolff-Goodell (on the basis of intensive study of their own p.t.'s) have concluded that there is a very narrow and constant range of the p.t. in human beings, our review of the literature,[9, 10, 18, 22, 28–30, 32, 35–38, 41, 43–46, 52, 56, 59] gathering together the work of many research workers, indicates that there is a significant range in the clinical p.t. when a sufficiently large group of subjects is tested, owing to such factors as: the characteristics of tissues stimulated (sweating, oiliness), the temperature of the skin, the pressure with which the head is held against the apparatus, degree of blackening and thickness of the blackening film on the skin surface, and other physical and physiologic factors concerning India ink, psychologic stresses, the anatomic area stimulated, type and thickness of underlying tissue, etc., which do operate clinically. These factors, particularly when they reinforce each other, are of real clinical importance in evoking or damping pain when radiant heat pain stimuli are applied. Hence, it is our opinion that for practical purposes the p.t. (using the HWG technique) of a large group of subjects may vary significantly clinically, even though it may also well be true, for instance, that in theory all subjects first feel pain when the temperature of their skin is raised to what approximates an equal level for all; this is a test condition, it is emphasized, concerning which Hardy-Wolff-Goodell were not aware when they concluded from experiments on themselves that the p.t. in man was uniform. Such exogenous factors, of course, are probably at work also in other methods designed to evaluate the p.t., its uniformity and constancy. A more detailed presentation of data obtained from our review of the literature concerned with the p.t. to radiant heat in human beings will be reported separately.

Reaction to pain is, of course, a most variable phenomenon. This latter factor, when further reinforcing different inherent and outside factors influencing the p.t., probably accounts for the clinical importance of any clinical variations in the p.t. noted.

There is also some evidence that the p.t. may be affected by various disease

states,[44, 45] although much additional controlled work would seem necessary and indicated in this area. The HWG technique may also be useful in establishing and measuring the painfulness of various diseases, and may perhaps be applied to the study of so-called psychosomatic pain.

Only very broad conclusions have been drawn by the present authors from the data presented. Evaluation of the particular usefulness of the technique for a specific future study or future problem has been left to the individual interests of those who intend working with the technique. An extensive bibliography is presen.ed.

SUMMARY

With certain broad reservations as to variations in the technique employed, training of subjects, and methods of statistical evaluation, the Hardy-Wolff-Goodell radiant heat pain threshold apparatus seems well deserving of its established preeminent position in the study of the physiology of pain and the pain threshold. An extensive review of the literature with regard to the uniformity and constancy of the pain threshold to radiant heat in human beings suggests that although under optimum conditions the pain threshold may perhaps be constant for an individual, there are apparently inherent endogenous and exogenous factors that produce clinically significant variations in the human pain threshold to radiant heat between individuals of a large group of normal subjects, even though it now appears that control of all such factors might result in more uniform findings.

In the study of analgesic agents in terms of their effect on the pain threshold, the accuracy and validity of conclusions concerning analgesic action in human beings drawn from the use of the Hardy-Wolff-Goodell radiant heat pain threshold apparatus and technique have been questioned by some investigators. This situation has arisen principally because of the complex problems of: controls and statistics; obtaining unbiased, disinterested, emotionally stable, unsophisticated, but highly trained subjects for double-blind investigations; and the site and mechanism of action of analgesic agents. On the basis of these difficulties (rather than on deficiencies in the method or instrument), the application of the Hardy-Wolff-Goodell apparatus and technique in the field of analgesic testing in human beings and the validity of conclusions drawn therefrom must still be considered a matter of some uncertainty at this time without reflecting unfavorably on its other uses.

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(Please turn to page 228 for Bibliography.)

NEW ANTIBIOTIC EFFECTIVE IN TUBERCULOSIS. Streptovaricin, a new antibiotic shown to be highly effective in destroying tubercle bacilli in laboratory tests, is now undergoing clinical trial, report scientists at The Upjohn Company. Tests showed the antibiotic (trade-named Dalacin by Upjohn) to be 10 times as active as streptomycin, 100 times as active as para-aminosalicylic acid (PAS), but only half as active as isoniazid, in experimental tuberculosis therapy. The new drug is now being tried clinically in combination with isoniazid.

"STOPPED HEART" OPERATIONS USED SUCCESSFULLY IN 100 CASES. "Stopped heart" operations, in which the heart is brought to a temporary standstill while an artificial device takes over the work of circulating blood to the rest of the body, have now been performed successfully in more than 100 cases, report surgical teams from Henry Ford Hospital, Detroit, and Cleveland Clinic, Cleveland. The technique allows the surgeon to work more freely and more safely deep inside the heart than ever before, enables him to repair life-shortening defects once held incurable.

NEW NYLON ARTERY BEING USED TO REPLACE HUMAN AORTA. A new nylon artery to replace the vital human aorta where it branches to carry blood to the legs has been placed in more than 200 persons, reports the Chemstrand Corporation, which developed the Y-shaped graft. Especially useful for patients with arteriosclerosis and in emergency replacement for accident victims, the nylon arteries have the advantage over human replacement arteries: are readily available, present no major preservation problem, contain no human tissue to become diseased, yet get along well with human tissues.

SUICIDE RATES STUDIED BY WORLD HEALTH ORGANIZATION. The highest death rates from suicides in both sexes are found in Japan, Denmark, Austria, and Switzerland; the lowest in Ireland, Northern Ireland, Chile, Scotland, and Spain, according to a statistical survey of suicides by the World Health Organization. Between 71,000 and 72,000 men and women commit suicide each year in the 25 countries studied (total adult population 400,000,000), with men having higher rates than women everywhere.

"FULL-RANGE" ATARAXIC NOW AVAILABLE. Perphenazine, a superior "full-range" ataraxic that can be used with increased effectiveness and relatively greater safety in all degrees

A New Trend in Medical Journalism

MD Medical Newsmagazine Launched in January

A dynamic new form of medical journalism was launched with the January, 1957, issue of the new medical newsmagazine, MD, published by MD Publications, Inc. Distributed monthly on a controlled circulation basis to 150,000 physicians in the United States, MD departs from the form of the usual medical journal and presents a unique approach to the medical, cultural, and social interests of the physician.

Félix Martí-Ibáñez, M.D., Professor and Director of the Department of History of Medicine, New York Medical College, is publisher and Editor-in-Chief of MD; Michael Fry, D.Sc., is News Editor. The following are the members of the Editorial Board: Conrad Berens, M.D., Francis J. Braceland, M.D., George W. Dana, M.D., John F. Fulton, M.D., Wallace E. Herrell, M.D., J. A. W. Hetrick, M.D., Frank Hinman, Jr., M.D., Norman Jolliffe, M.D., Perrin H. Long, M.D., Jacques M. May, M.D., W. F. Norwood, Ph.D., Alton Ochsner, M.D., Winfred Overholser, M.D., Linus Pauling, Ph.D., Edwin J. Pulaski, M.D., Charles R. Rein, M.D., Hans Selye, M.D., Henry Welch, Ph.D., and Irving J. Wolman, M.D.

In an Editor's message in the first issue of the newsmagazine, Dr. Martí-Ibáñez states that the purpose of MD is "to satisfy the physician's curiosity about the vast, rich tapestry of medicine *and of life*. MD regards the physician as a man of many personalities. He is not only a professional but also an individual and a member of society. As a professional, he is interested in the art and science of healing; as an individual he feels the need to increase his general cultural knowledge; as a member of society he wants to understand the political, economic, and sociologic, as well as the public health problems of his community, his country, and the world in general. A physician is not only a social person; he is also a *historical* person. The interests of the world therefore are his interests. . . . True to Osler's words, MD will 'create, transmute and transmit' news and events for the physician. It will inform him, guide him, and entertain him."

Featured sections of MD are *World of Medicine*, reporting all the important news in medicine and written by clinical experts and special correspondents in the medical centers of the world; *Medicine in the World*, presenting world events affecting the physician and medicine and featuring physicians as creative citizens; as sportsmen, musicians, artists, writers, statesmen, and travelers; and *Medicine in the Arts*, which describes the contribution made by the arts to medicine and also medicine's contribution to the arts, featuring departments on music, books, theatre, art, cinema, and radio-television.

More than 1500 letters praising the new magazine were received after publication of the first issue, which featured a story relating childhood background to adult achievements of Nobel laureates. White House physicians were the subject of the February cover story, and other interesting features planned for future issues include stories on space medicine and on food and cooking. Further information about MD may be obtained from the publisher, MD Publications, Inc., 30 East 60th St., New York 22, N. Y.

BACKGROUND TO NEW THERAPIES

Reserpine

Development and Future Perspectives

HISTORY POINTS THE WAY

In 1582 Leonard Rauwolf published a report of his study of medicinal plants of Asia and Africa. He had returned from an expedition to study plants that had been described by Greek and Arabian physicians. Recognition of his work was almost immediate and subsequently a new plant genus was named *Rauwolfia*.

One species of the approximately 50 members of the genus, *R. serpentina*, has its medicinal origin in ancient India. It is the most important member, known because of its unique medicinal properties.

For centuries in India, "snake root" was used for snake bite and dysentery. Its use in these conditions later led to its use in a variety of disturbed mental and emotional states loosely grouped under the diagnosis of "insanity." Until the seventeenth century, it was recognized as valuable in treating "anxiety states."

Like many ancient remedies, however, its use in India was largely ignored by the rest of the world until the early 1930's when two chemists named Siddiqui reported in the *Journal of the Indian Chemical Society* their isolation of a crystalline alkaloid. Then in 1933 Chopra, Gupta, and Mukherjee reported their pharmacologic studies indicating the hypotensive activity of extracts obtained from *R. serpentina* roots.

Following their report, many workers experienced a rekindled interest, and work progressed in many laboratories. Then in 1952 Mueller, Schlittler, and Bein isolated and reported an alkaloid that they named reserpine. It was remarkable because of its potent sedative and hypotensive properties. These two effects are indicative of the two major body systems responding to reserpine, i.e., the central nervous system and the cardiovascular. Numerous investigations point to the hypothalamic centers as the primary site of action. All of the pharmacologic effects observed, such as cardiovascular changes, alterations in emotional response, peripheral autonomic changes, and sedation, appear to be accounted for on the basis of inhibiting the sympathetic predominance at the hypothalamic level in the central nervous system.

SOME BASIC REFERENECS

1. *Human Pharmacology of Reserpine*. Travis Winsor. Annals of the New York Academy of Sciences. Vol. 59, Art. 1, page 61, 1954.

The author reports the effects of reserpine on the cardiovascular, nervous, and endocrine systems of hypertensive patients. Sixty-five patients, 55 per cent men,

This article is reprinted from *Antibiotic Medicine & Clinical Therapy* 4:108–113, Feb., 1957.

were included in the study. The average age was 50 years. Ninety per cent had benign or essential hypertension, 6.7 per cent had malignant hypertension, and 3.2 per cent had renal hypertension associated with mild chronic glomerulonephritis. All drugs, including reserpine, were tested using the double-blind technique. The findings indicate that a large dose of reserpine produced a greater fall in systolic and diastolic blood pressure and pulse rate than did a small dose. Large doses were not well tolerated, since more than 50 per cent of the patients experienced side effects severe enough to warrant a reduction in dosage. With a small daily dose (average 0.4 mg. daily) only 25 per cent of patients had side effects of a minor nature. The greatest fall in diastolic blood pressure occurred in patients between the ages of 30 and 50. There was no discernible difference in response on a sex basis. Individuals with hypertension for 2 to 10 years showed the greatest fall. Diastolic levels from 111 to 160 likewise showed the greatest reduction. Patients with albuminuria showed a greater fall than those without albuminuria. Patients with grade IV eye ground changes responded with a greater fall in pressure than those in grade O, I, II, or III. In general, the more severe the signs and symptoms of cardiovascular disease, the greater the reduction in diastolic pressure produced by reserpine. The action of reserpine was enhanced by combining it with hydrazinophthalazine which acts, at least in part, on the kidney. In some cases the addition of azamethonium was more effective than the latter two alone. The site of action of reserpine is, in part, on the subcortical regions of the brain, possibly the hypothalamus, as shown by the blocking of inspiratory and pain reflexes after large doses of the drug.

2. *Clinical Usage of Rauwolfia Alkaloids Including Reserpine.* Robert Wilkins. Annals of the New York Academy of Sciences. Vol. 59, Art. 1, page 36, 1954.

Rauwolfia and reserpine are useful additions to the medical treatment of hypertension. Both drugs, the author reports, cause sedation, bradycardia, hypotension, nasal stuffiness, weight gain, and, in excessive doses, diarrhea, nightmares, and agitated depression. They have a marked additive or perhaps even synergistic effect when administered in combination with other hypotensive agents. Perhaps their most important beneficial effects are observed in the reduction of "neurotic" symptoms in all treated patients and the lowering of blood pressure, particularly in young labile neurotic hypertensives with tachycardia. The author also states the drugs can be taken apparently indefinitely and do not result in tolerance or addiction.

3. *Use of Reserpine in a Neuropsychiatric Hospital.* Nathan S. Kline and Alfred M. Stanley. Annals of the New York Academy of Sciences. Vol. 61, Art. 1, page 85, 1955.

The author reports on more than 1500 patients treated during a year and a half of investigative experience. The number of assaults, the number of restraints and seclusion, and general noise level were all decreased as a result of reserpine administration. In general, patients became more cooperative. The drug has proved effective where other recognized sedatives have failed. Danger from overdosage compared with other medications used for sedation is minimal. The drug, effectively used, has materially changed and improved patient demeanor on the wards, thereby permitting nurses and attendants to concentrate more on constructive activities instead of being preoccupied with custodial care.

It is important to remember that patients go through three phases in therapy: the sedative, the turbulent, and the integrative. While they may appear worse in the turbulent phase, it is not usually an indication for discontinuing treatment. Some patients who fail to respond favorably on the first course of reserpine respond quite well to a second course or by combining reserpine and chlorpromazine.

Approximately 5 per cent of patients developed parkinsonism, which was reversible when dosage of reserpine was reduced.

The author states, "It appears probable that it [reserpine] will shorten the duration of hospitalization economically, and will permit the discharge of patients formerly deemed unmovable, and we already know that it serves to make more comfortable those patients who must remain hospitalized. It would seem that the next major field for exploration would be to determine whether use of the drug might not serve to prevent the number of patients requiring admission to mental hospitals."

4. *Clinical Effectiveness of Reserpine.* Frederic F. Flach. Annals of the New York Academy of Sciences. Vol. 61, Art. 1, page 161, 1955.

Nineteen patients were included in the study. Two manifested acute schizophrenic reactions; 6, chronic schizophrenic reactions; and 9, severe depressions. Beneficial effects were usually observed in the first three to eight days of therapy in those patients who did respond. When the ultimate clinical effect was considered only "fair" beneficial changes were slower in appearance, occurring gradually over a period of one to three weeks.

When tension, fear, and anxiety with somatic components are prominent, reserpine appeared to provide decided relief. The drug does not seem to quell or exaggerate elation, whether present initially or occurring in the course of treatment replacing depressive reaction. The physician must give special consideration to somatic sensations induced by the medication that the hypochondriacal or hysterical patient may use to change or negate the other beneficial effects of the drug.

Verbalization was improved such that patients were able to reveal serious psychopathology previously hidden.

Bradycardia, seen in most cases, often is a therapeutic problem. In cases of severe depression, the decreased responsiveness of the autonomic nervous system induced by reserpine increases the risk of cardiac complications in electroshock therapy.

5. *The Tranquilizing Efficacy of Reserpine in Dermatological Therapy.* Charles R. Rein and J. John Goodman. Annals of the New York Academy of Sciences. Vol. 61, Art. 1, page 230, 1955.

This study of a group of 60 selected patients in whom there was an uncontrollable urge to scratch or in whom a psychic or nervous factor appeared to contribute to the skin disease. Forty of the group obtained unequivocal relaxation, sedation, tranquilization, and decrease of anxiety and inner tension.

Ataractic drugs are of great value, report the authors, to the dermatologist in conducting the management of patients with widespread pruritic dermatoses.

It should be emphasized, however, that reserpine obviously does not constitute definitive therapy for the cutaneous disease. It does constitute a valuable therapeutic adjunct.

6. *Current Status of Chlorpromazine and Reserpine in Psychiatric Practice.* Burtrum C. Schiele, Richard W. Anderson, and Werner Simon. *The Journal Lancet.* Vol. 76, No. 7, page 179, 1956.

Reserpine is an effective hypotensive drug exerting its action centrally producing evidence of parasympathetic predominance. It does not produce ganglionic or adrenergic blocking effects and does not alter postural reflexes. Reserpine abolishes the sham rage phenomena supporting the hypothesis that the drug increases cortical inhibition of brain stem structures. Parkinsonian symptoms occur in patients on chronic therapy at high dose levels and the convulsive threshold in electroshock therapy is reduced by reserpine.

The authors report that complications are less frequent and less severe than those produced by chlorpromazine. The most important are the parkinsonian-like syndrome which is reversible on withdrawal or reduction of dosage. Complete disappearance usually requires 10 to 20 days. Some physicians feel that chronic patients only begin to manifest improvement with the onset of parkinsonian symptoms and hence are reluctant to stop reserpine therapy. Such symptoms usually can be adequately controlled by a slight reduction in dose and administration of methanesulfonate or a similar agent.

Depressive reactions are reported by several observers, being either mild or severe. Most frequently they occur in patients with a previous history of depression or long-standing tension and anxiety. It is important to recognize signs and symptoms of a depressive reaction as early as possible. Most respond favorably to withdrawal of reserpine, psychotherapy, and electroshock. Cortical stimulants, such as amphetamine, are useful in therapy. Mental confusion occurs rarely, is serious, and usually requires cessation of reserpine therapy.

The ability of these drugs to induce tranquilization without clouding of consciousness makes them unique therapeutic agents. Their use reduces the necessity for using more rigorous methods of treatment, such as shock therapy (both insulin and electroshock) and lobotomy. All patients, however, do not benefit.

Reserpine, according to the authors, is slower in its onset of action, less potent but less toxic than chlorpromazine.

The use of these drugs in acute states has been well established. Benefits to chronic patients occur but are less consistent. Long-term use of the drugs to maintain improvement necessitates additional experience and evaluation.

7. *Chlorpromazine and Reserpine; Symposium on Experiences at Saint Elizabeths Hospital. Reserpine.* Francis N. Waldrop. Medical Annals of the District of Columbia. Vol. XXV, No. 5, page 256, 1956.

Approximately 700 patients have been treated with reserpine for periods of one month or more.

Usually patients were selected on the basis of behavioral criteria because of being "agitated, destructive, assaultive, noisy, combative and overactive" rather than on the basis of psychiatric diagnosis. Maintenance doses varied from 0.5 to 10 mg. daily with an average of 2 mg. daily. When the tranquilizing effect occurred, maintenance doses varied widely and had to be individualized.

Approximately 13 per cent of the patients did not respond favorably after a full

month of treatment. Many, however, were chronic patients hospitalized for more than five years. Some of these patients might benefit if the drug had been continued longer or the dose increased.

About 62 per cent of the patients received a good response and became more cooperative and manageable. Despite the good tranquilizing effect, these patients still retained their basic core of mental illness as manifested by delusions, hallucinations, confusion, disorientation, and disordered emotional response.

Twenty-five per cent of the patients treated with reserpine not only achieved a good tranquilizing effect, but also revealed a definite reduction in abnormal content, such as delusions and hallucinations. Almost all patients in this group were diagnosed schizophrenic in one form or another.

Approximately 40 per cent of reserpine-treated patients who responded favorably have suffered a partial or complete relapse when reserpine was discontinued. Some patients, however, retained their improvement for as much as six months and are still progressing satisfactorily without medication. As yet no pattern or criteria have been found which permit one to predict which patients will relapse in short order and which will not when reserpine is stopped.

In 7 per cent of patients reserpine was discontinued due to somatic side effects, with a higher incidence in women than in men. In 4 per cent reserpine was stopped because of psychiatric complications, most important being depression or a toxic confusional state.

8. *Chlorpromazine and Reserpine in Psychiatric Practice.* Winfred Overholser. *Postgraduate Medicine.* Vol. 19, No. 4, page 346, 1956.

The action of reserpine is not particularly rapid, is cumulative, and is safe. Indications for use in psychiatry are "conditions in which anxiety, tension, aggressiveness and excitement occur." The patient becomes more accessible to psychotherapy. Nevertheless, despite the improvements in some aspects of hospital management of disturbed patients, these drugs require the exercise of skill and imagination by physicians and hospital staff members to provide necessary psychiatric treatment for patients no longer acutely disturbed. These drugs are very valuable in the treatment of institutionalized patients. Long-term results must be evaluated carefully.

9. Rauwolfia serpentina *in the Treatment of High Blood Pressure. A Review of the Literature.* Rustom Jal Vakil. *Circulation.* Vol. 12, No. 2, page 220, 1955.

Investigators in many countries all confirm the hypotensive effects of *R. serpentina* and also of reserpine, the most active alkaloid contained in the crude root. There is no serious disagreement as to observed side effects. This paper contains an extensive list of references.

10. *Use of Chlorpromazine and Reserpine in the Treatment of Emotional Disorders.* William W. Zeller, Paul N. Graffagnino, Chester F. Cullen, and H. Jerome Rietman. *Journal of the American Medical Association.* Vol. 160, No. 3, page 179, 1956.

Reserpine and chlorpromazine were found to be equally effective in the treatment of patients in a private psychiatric hospital. Reserpine produces more unpleasant and annoying side effects to the patient, but it is a safer drug than chlorpromazine in the opinion of the authors. It is less rapid in onset, however. Both are interchangeable in the treatment of most patients. The psychiatric diseases for which

these drugs are reported to be of clinical value in descending order are: manic-depressive psychosis (manic phase); agitated states, particularly those associated with organic brain disease; schizophrenia; depressive reactions; and neuroses.

NEW PERSPECTIVES AND FUTURE RESEARCH

The advent of each new group of drugs in the history of medicine has given rise not only to better medicines for physicians and their individual patients, but each in turn has opened new vistas for research and understanding of life processes, both normal and pathologic. Perhaps no group of compounds has provided the stimulus, pointed the way, and enticed the investigator to the extent that the tranquilizers have done in the last five years. While long-range studies must be undertaken and results exhaustively evaluated, their clinical use has already proved to be valuable if not almost indispensable.

The seemingly impenetrable barriers to an understanding of mental disorders at last appear to have been successfully assaulted. To reduce emotional and mental disease to a biochemical basis is fundamental to the development of an integrated picture of its physiological, pharmacological, and pathological responses. Progress, both fundamental and clinical, is to be anticipated.

SUMMARY

Reserpine, an alkaloid of *Rauwolfia serpentina*, has been extensively used since its isolation in 1952 because of its potent sedative and hypotensive properties, the effects of which seem to occur at the hypothalamic level in the central nervous system. Hypertensive patients with neurotic symptoms and tachycardia benefit greatly from use of the drug as do acutely ill schizophrenic patients. As a therapeutic adjunct in skin disease, reserpine helps to relax and decrease anxiety and inner tension so that the cutaneous condition is amenable to therapy.

The major side effect seen is the parkinsonian-like syndrome, which is reversible with reduction or withdrawal of dosage. Depressive reactions, mild or severe, respond to withdrawal of the drug, psychotherapy, and electroshock. Mental confusion, which occurs rarely, necessitates withdrawal of reserpine.

Despite the good ataractic effect, long-term use of reserpine to maintain improvement and the selection of patients who will respond favorably to use of the drug are areas in which additional experience and evaluation are needed.

BOOK REVIEWS

Modern Nutrition in Health and Disease. Edited by MICHAEL G. WOHL, M.D., AND ROBERT S. GOODHART, M.D. 55 contributors. Philadelphia, Lea & Febiger, 1955. 80 illustrations. Price $18.50.

This new edition presents the salient advances in nutrition that have a direct bearing on optimal health and the prevention and treatment of disease. It is written by 55 authorities representing each branch of medicine. The book is comprised of three parts: normal nutrition, nutrition in disease, and nutrition in distress. The approach is physiologic throughout, with strong emphasis on the role of diet in the prevention and treatment of disease. New chapters have been included on body composition, psychology of hunger, antimetabolites, hormonal control of metabolism, and the newer B vitamins. There are also pertinent discussions of nutrition in neurology and psychiatric treatment, emergency feeding, and specific nutritional indications in the various specialties. The book is well integrated and reads as if it were produced by a single author. It is the best guide to nutrition in medical literature.—*I. Newton Kugelmass, M.D.*

Transport and Accumulation in Biological Systems. E. J. HARRIS, PH.D., D.I.C., D. SC. New York, Academic Press, Inc., 1956.

This volume represents the result of an attempt to gather together some of the extensive information that has been published recently on the subjects of cellular inorganic chemistry and the kinetics of movement of inorganic and simple organic substances between cells and their surroundings. The advent of radioactive tracers and the development of flame photometry as an analytic tool accounts for the progress in the field of cell permeability, but the mechanism of the nervous impulse has been elucidated by quite different methods with results of fundamental importance.

Almost any process involving cells and substances can be formulated in terms of permeability or adsorption coefficients; hence little excuse is needed for limiting the subject matter to selected examples. References to the literature have mainly been to later work, for such papers themselves provide earlier references when these are required. The range of chapters includes: "Membrane Structure and Penetration"; "Factors Governing the Distribution and Movement of Water"; "Movement of Water, Factors Governing Ion Distribution"; "Blood Cells"; "Passage of Water and Salts through Amphibian Skins"; "Muscle"; "Mitochondria"; "Ion Contents and Movements in Various Tissues"; "Nonmyelinated Nerves"; "Medullated Nerve"; "Plant Cells and Yeast." This is a remarkable summation of recent advances in the field and a concisely integrated physicochemical mechanism involved in transport in biologic systems.—*I. Newton Kugelmass, M.D.*

ADVANCED REPORTS FROM CURRENT MEDICAL MEETINGS

This section of the INTERNATIONAL RECORD OF MEDICINE features reports on papers delivered at current medical meetings in the United States and abroad.

Increase in Frequency of Leukemia

Berlin.—The frequency of leukemia is rising steadily all over the world, says Paul Vlamynck (Stadtisches Krankenhaus Köpenick, Berlin), especially in civilized countries such as the United States. In 1954, leukemia ranked fourth among the causes of death of children less than 14 years old in New York City. The increase includes both acute and chronic leukemia. As in the case of carcinoma of the lung, this is a true increase, not due just to "improved methods of diagnosis," as it has been evident even during the last 10 years without great advances in diagnosis. Among the etiologic factors, he includes, in addition to "civilization" and atomic explosions, a true genetic factor. In mice, morulas have been transplanted from leukemic strains to nonleukemic strains, thus causing leukemia in the latter. The observation that 75 per cent of children with acute leukemia are first-born may point to a maternal factor of resistance developing through pregnancies. The thymus gland also plays a role in the human being: after irradiation of the gland a 7 per cent higher incidence of leukemia was found. Food may also be a factor, since veterinarians have found more leukemia in animals on a high protein diet. Also, it is possible to reduce this figure by reducing the protein. Other factors include geographic distribution, viruses, and carcinogens. Also proved is the importance of irradiation, for which there was found a definite proportion between incidence and dose. Stewart found that for 269 cases of leukemia in children, 15.6 per cent of the mothers had had abdominal roentgen-ray examinations during pregnancy. Polycythemia may also develop into leukemia, especially after isotopes have been used (P^{32}). Radiologists get leukemia nine times as often, physicians 1.7 times, as the rest of the population.

(Presented before the meeting of the Berlin Radiologic Society, Berlin, Jan. 29, 1957.)

Hip Fusion in Ambulatory Patients

Chicago.—A method of hip fusion in which the patient is ambulatory on crutches without any form of external fixation and is discharged from the hospital two weeks after surgery is presented by Howard W. Schneider (Northwestern University Medical School and Cook County Hospital, Chicago). The technique uses intra-articular hip fusion, iliac bone grafts, and intramedullary nail fixation. The sole fixation device is a curved, 4 flanged nail, which extends from the posterior iliac spine through the body of the ilium, across the hip joint, into the medullary canal of the upper two thirds of the femur. According to Dr. Schneider, the nail produces 14 cm. of fixation to the body of the ilium and at least twice this length of fixation within the femur.

"The position of the nail in the ilium utilizes the maximum length of fixation in the strongest part of the bone," Dr. Schneider declares. "The snug fixation is obtained by using the self-cutting type nail, which in itself acts as the cutting instrument in preparing its bed in both the ilium and the femur." Also, he says, the 4 flanged shape of the nail gives antirotational fixation as well as maximum strength for its weight. The nails are 10, 11, or 12 mm. wide and from 42 to 48 cm. long. A curved nail is used, he says, to obtain the desired position.

The presentation included results in a series of 10 cases in the past three years of patients with conditions such as osteoarthritis, rheumatoid arthritis, old hip dysplasia, old fracture of the neck of the femur, and childhood disease of the hip, who presented with pain or pain instability. The one failure in the series was a patient with an old fracture of the neck of the femur and amyotrophic lateral sclerosis. All patients in the series were ambulatory in from 2 to 14 days after surgery and remained in the hospital 14 to 17 days.

"The postoperative management," Dr. Schneider declares, "is surprisingly easy." The patients are able to turn from side to side and handle themselves in bed with the aid of a trapeze the first few days. They sit up after the fourth day and become ambulatory with the aid of crutches and partial weight bearing by six to eight days postoperatively. A few of these patients were able to discard all support four weeks postoperatively.

(Presented before the American Academy of Orthopedic Surgeons, Chicago, Jan. 26–31, 1957.)

Fat Embolism

Chicago.—Basic and clinical studies on fat embolism in more than 1000 patients with long bone fractures were carried out at the University of Minnesota by Leonard F. Peltier (Head of Section of Orthopedic Surgery, University of Kansas School of Medicine). Fat embolism, he says, may occur in as many as 60 per cent of patients with severe long bone fractures. It can range from a minor condition, to a state of coma and dyspnea, to death. When it is suspected, he notes, the surgeon should order microscopic urine examination for fat droplets.

Fat embolism can be markedly reduced or even prevented by adequate care of these patients, Dr. Peltier says. Such care should include prevention of shock by gentle handling of fractures, replacement of whole blood, plasma when necessary, and relief from pain; the use of a tourniquet when opening fractures; gentle handling of tissues; and proper splinting in transport, including trips for roentgen examination. Bone, because of its high fat content and its large network of blood vessels, provides an ideal setting for invasion of fat droplets into the general blood stream after injury, Dr. Peltier points out.

(Presented before the American Academy of Orthopedic Surgeons, Chicago, Jan. 26–31, 1957.)

Salk Vaccine for Entire Population

Pittsburgh.—At the American Medical Association Salk Vaccine Meeting, Jonas E. Salk (Pittsburgh) pointed out that while the primary emphasis of the Salk vaccine program is inoculation of the 0 to 39 year age group, it might be time to start thinking of inoculating the entire population to eliminate the 4 or 5 per cent of vulnerable persons in the older groups. Vaccinating the great majority of the public will not protect the unvaccinated.

"There is no reason why there should be any poliomyelitis in 1957," says Dr. Salk. He is still hopeful that there will be a permanent persistence of immune response in the series of three inoculations, but says that if any physician wishes to give a booster dose each year, no harm can be done. Some of Dr. Salk's control subjects have had as many as six inoculations.

Dr. Salk also says that if a child has received a first inoculation but never a second it is not necessary to start the series over. The physician should proceed with the second, and then give the third at least seven months afterward for best results.

(Presented before the American Medical Association Salk Vaccine Meeting, Chicago, Jan. 26, 1957.)

Amino Acid Metabolism of the Brain

Bethesda, Md.—Pyridoxine and glutamic and aspartic acids, and their derivatives, are emphasized as being of vital importance in the amino acid metabolism of the brain by

Donald B. Tower (Department of Clinical Neurochemistry, National Institutes of Health). He reports a series of metabolic experiments using animal brain substance and isotopic labeled amino acids and carbohydrates, which showed that aspartic acid, glutamic acid, gamma aminobutyric acid, and serine are among the substances in heaviest concentration in brain tissue.

Studies of young and adult animal brain tissue further indicated the importance of the blood brain barrier in metabolic exchange. The barrier begins to be effective at about the age of 3 to 4 months, and then increases in selectivity through adulthood. In a series of experiments in which various amino acids were infused intravenously, significantly increased levels in the brain substance were shown only by asparagine and glutamic acid. Similar studies showed that of the total free amino acid pool in brain substance, more than 75 per cent consisted of glutamic and aspartic acid derivatives. During convulsive seizures caused by an irritative cortical focus, the values for glutamic acid and pyridoxine were significantly decreased, and the injection of large amounts of this vitamin was enough to stop the convulsions immediately. Control of experimentally induced seizures was likewise achieved by mixtures of glutamic and aspartic acid and pyridoxine. The significance of pyridoxine for neuronal metabolism is further shown by its toxicity to the nervous system if present in too great concentration. It is the only one of the B complex group that has this effect.

Isotopic studies revealed further that the rate of exchange between the blood and brain in metabolism of amino acids is the same in childhood as it is in adulthood, but as the blood brain barrier becomes effective with age, there is a net gain of the amino acids indicated in the cerebral substance. With this shift in function of the barrier, there is a concomitant shift to the carbohydrate phase of synthesis of amino acids. C^{14}-labeled carbon atoms, administered in the form of glucose and pyruvates, are found in much greater amounts in the form of glutamic and aspartic acid derivatives in the adult brain, in comparison with that of young or newborn animals. Further work to determine the relative concentrations and localizations of the various amino acids is under way, Dr. Tower indicates, and better understanding of the biochemistry of the functioning of the brain will certainly follow such research.

(Presented before the Conference on Protein Metabolism, Rutgers University, New Brunswick, N. J., Jan. 25-26, 1957.)

Diagnosis of Cushing's Syndrome

Nashville, Tenn.—A new tool in the diagnostic evaluation of Cushing's syndrome, based on the fact that normal persons have suppressible 17-hydroxycorticoid-producing mechanisms while patients with Cushing's syndrome do not, is reported by Grant W. Liddle for a team from Vanderbilt University School of Medicine (Nashville). Normal subjects given 0.5 mg. every six hours by mouth of delta-9 alphafluorohydrocortisone showed negligible levels of corticoid secretion and excretion by the second day of suppressive treatment, Dr. Liddle says. On the other hand, he notes, 16 patients with Cushing's syndrome all showed complete resistance to suppressive treatment. This was true whether the etiology of the Cushing's syndrome was bilateral adrenocortical hyperplasia, benign adrenocortical adenoma, or adrenocortical carcinoma.

(Presented before the meeting of the Southern Section, American Federation for Clinical Research, New Orleans, La., Jan. 25, 1957.)

Genetic Aspects of Diseases of Metabolism

New York City.—"Agammaglobulinemia, hemophilia, and phenylketonuric oligophrenia are among a group of genetically determined diseases that are now amenable to treatment since the genetically conditioned defects are well understood," says Alexander G. Bearn (Associate of the Rockefeller Institute, New York City). "Contrary to

formerly held theories, congenital or genetic defects are definitely amenable to therapy, of course within limits, provided the metabolic or enzyme defects are studied and their nature understood," he says. "The provision of gamma globulin will cure agammaglobulinemia, antihemophilic globulin will alter the picture in bleeders, diet low in phenylalanine will save children from the complications of phenylketonuric dysfunction," he continues.

"Not all inherited diseases are visible at birth, and many forms of hereditarily determined abnormalities are now being discovered. Many of the latter are completely innocuous, as far as can be determined today," Dr. Bearn says. Forty-six of 115 persons studied produce a substance known as methanediol after ingestion of asparagus, a substance that renders their urine malodorous. Ten of 104 patients have a reddish colored urine after eating beets. Alkaptonuria, a well known disease of metabolism, is another example of a hereditary condition.

From the studies to date, it appears that some enzyme systems are determined by a single gene. Among these are diseases involving lack of specific enzymes, such as catalase (in a family of 5 persons reported in Japan), galactase (in the well known pediatric disease of galactosemia, recently explained as due to a congenital lack of this enzyme), and perhaps Wilson's hepatolenticular degeneration. The defect of copper metabolism in the latter is perhaps due to an enzyme lack in the cycle of copper metabolism. "What is already known of phenylketonuria and Wilson's disease makes one wonder how many other patients are in mental institutions because of our inability to discover the metabolic fault involved," Dr. Bearn says. Effective therapy would very likely consist in supplying the enzyme lacking in many of these conditions, but the difficulties involved preclude such an approach at present. We are, therefore, limited to attempting to substitute, by means of diet, for the substances incorrectly metabolized. This is best illustrated by the phenylalanine-free or low content diets now offered to children affected with this condition. Further research along these lines will certainly aid in clarifying many metabolic problems of a similar nature.

(Presented at the Jewish Chronic Disease Hospital, Brooklyn, N. Y., Jan. 24, 1957.)

Influence of Emotional Factors in Gastroenterology

Boston.—The gastrointestinal tract has a preponderant array of symptoms in which emotions play a role, states Franz J. Ingelfinger (Assistant Professor in Medicine, Boston University; Physician, Massachusetts Memorial Hospitals). Fifty per cent of gastrointestinal tract complaints have an emotional overlay. Of these, 80 per cent fall into one of four groups.

1. Anxiety states with fixation on the digestive tract. These patients have very minor or no real symptoms. They are neurotics who fix on the gastrointestinal tract and are usually very concerned about the significance of belching and bowel movements. This group also includes the patients with fear of cancer. Treatment of this group is difficult. Dr. Ingelfinger's approach is to explain to the patient that he can have symptoms without underlying disease. Explain that tensions can cause symptoms, but be careful not to suggest to the patient that he is imagining symptoms. The ataraxics have a definite place here.

2. Functional disorders. In this group the patients have a normal gut, but the function is deranged. They have spasms and lack of coordination of the gut, which produces cramps, heartburn, and constipation. It is difficult to determine how much of the symptomatology is due to emotional overlay. Treatment has two facets: (a) treatment of the immediate motor disorder by dietary and pharmacologic preparations as indicated and (b) treatment of the emotional factor. At present it is best not to use the ataractic drugs because their entire pharmacologic effects on the gut are not yet known. They might interfere with the

functional disorder that is already present.

3. Peptic ulcers of esophagus, stomach, and duodenum. There is no doubt that emotional stress and strain affect this disease. During the London blitz of 1944, acute ulcer perforations increased fourfold. There has been a change in ulcer perforation over the past 50 years. In 1890 this was a disease of women; today it is a disease of men. One report from London concluded that if emotional stress is responsible for acute perforation, the English man was six times as disturbed in 1941 as his grandfather was in 1890, while the woman was only 1/200th as disturbed. Although emotions play a marked role in this disease, it does not respond well to psychiatric or pharmacologic therapy. The ulcer patient often is of a personality type that does not accept psychiatric help. Relief can be provided by strict medical management, regardless of the personality. This is the treatment of choice.

4. Regional ileitis and ulcerative colitis. These patients have severe emotional problems. An integral part of the therapy of this group is psychotherapy; ataractic drugs may be helpful in treating this group.

(Presented at the Bingham Associates Program for Postgraduate Medical Education, Boston, Jan. 14, 1957.)

Influence of Emotional Factors in Dermatology

Boston.—Emotional states can produce pallor, flushing, sweating, itching, and urticaria, and emotional problems in the treatment of skin disorders are common, states James F. Patterson (Assistant Professor in Medicine, Tufts College Medical School; Physician, New England Center Hospital). Emotional tensions may cause or aggravate conditions, and skin diseases in themselves produce emotional disturbances.

The psychic influence on skin disorders can be divided into four groups. (1) True psychogenically induced disorders are: factitial dermatitis, self-induced damage to skin, neurotic excoriations, compulsive digging at certain areas. (2) Emotions play an important role in the cause or continuing course of: anal and vulval pruritus, acne rosacea, lichen planus, chronic urticaria, neurodermatitis (atopic eczema). (3) Emotions may play a role in: seborrheic dermatitis, acne vulgaris, vitiligo, hyperpigmentation, alopecia areata. (4) Some diseases produce emotional disorders. Acne vulgaris in the adolescent is the most common, but almost any disease of the skin can produce emotional problems, including "dishpan hands."

For treatment of the emotional problems it is necessary to get a good history to try to evaluate the problem. This is done by showing interest in the patient and allowing him to speak. The treatment of the skin disorder will often, in itself, relieve emotional problems. Barbiturates, antihistaminics, and ataraxics may all be of value. It must be remembered, however, that these drugs can themselves produce eruptions.

(Presented at the Bingham Associates Program for Postgraduate Medical Education, Boston, Jan. 14, 1957.)

Influence of Emotional Factors in Medical Gynecology

Boston.—Menstruation, reproduction, and menopause produce and are altered by emotions, says Joseph Rogers (Assistant Professor in Medicine, Tufts College Medical School; Physician, New England Center Hospital). The psyche plays a marked role in many gynecologic problems.

Amenorrhea. Hypothalamic or psychogenic amenorrhea is absence of menstruation caused by emotional factors. This usually occurs in young women overworked at school, being separated from their husbands, or undergoing other emotional stress. The reproductive system is normal but the vaginal smears show evidence of hypoestrogenism. It is postulated that psychic factors affect the hypothalamus, which in turn blocks the release of luteinizing hormone. This type of amenorrhea usually does not respond to estrogen-progesterone for with-

drawal bleeding. Simple psychotherapy may bring immediate relief. Even a simple laboratory test or physical examination may produce menstruation. There is an increased incidence of amenorrhea among obese women; obesity is considered an emotional disorder. Simple treatment of the obesity often returns normal menstruation.

Menorrhagia. Functional uterine bleeding has been described as the "weeping of a disappointed womb." There is failure of ovulation due to low levels of estrogen and lack of progesterone. Functional uterine bleeding has often been resolved by release from emotional tension. The use of estrogen to produce withdrawal bleeding may also be helpful.

Dysmenorrhea. In the majority of cases there is no local pathology to explain symptoms. This is called primary dysmenorrhea. Patients who suffer menstrual pains often have headache, backache, gastrointestinal upsets, often associated with psychogenic causes. The patients have a low threshold to pain, and in many cases they have had poor prepubertal instruction and preparation for menstruation. Simple explanation and reassurance is often all that is necessary.

Premenstrual Tension. Some women suffer gastrointestinal symptoms, depression, headaches, and other symptoms two to three days before menstruation. This period is associated with physiologic water and electrolyte retention, and the symptoms may be related to this. Dr. Rogers feels that in many cases emotional factors lead the woman to overreact to physiologic changes, and these often respond to mood-tranquilizing drugs.

Infertility. That emotions play a large role in infertility is evidenced by the fact that any psychogenic support may lead to immediate pregnancy. This may be only an interview or physical examination. Emotional problems should be looked for and solved.

Habitual Aborters. Recently psychiatric therapy was given to a group of these women with 83.7 per cent success.

Pseudocyesis. This usually occurs in women with an intense desire to become pregnant or to avoid pregnancy. Menstruation ceases, the abdomen enlarges, morning sickness may develop—all produced by emotional factors.

Menopause. A woman may have marked difficulty at this time of her life. She often develops all forms of emotional problems and symptoms. The emotional problems are usually the result of her feeling that this is a change in her life, not merely hormonal change. A thorough examination and explanation are usually enough to help her. Occasionally estrogen is necessary to relieve the hot flashes.

(Presented at the Bingham Associates Program for Postgraduate Medical Education, Boston, Jan. 14, 1957.)

Influence of Emotional Factors in Cardiology

Boston.—Heart disease is the leading cause of death in this country; also, the lay person considers the heart the single most important organ, says Louis A. Selverstone (Assistant Professor in Medicine, Tufts College Medical School; Physician, New England Center Hospital). These two facts make the diagnosis of heart disease terrifying and may lead to all kinds of emotional problems. The diagnosis of heart disease from minor electrocardiographic changes can produce a cardiac ripple. Emotions affect the physiology of the circulatory system. Patients with cardiac failure have a fixed cardiac output. These patients may be thrown into pulmonary edema by emotional upsets. Blood pressure can also be dramatically influenced by emotional stress. There are many people with "doctor's office hypertension." True hypertensive headaches are rare; most appear to be tension headaches of psychogenic origin. The effect of emotional stress on angina pectoris has been noted since the disease was described by Heberden. Early in the disease, physical exertion plus emotional stress is required to produce symptoms. A vicious cycle is easily

set up: symptoms lead to apprehension; apprehension predisposes to further attacks. This can lead to angina decubitus. Sometimes ataractic drugs given with cardiac drugs are helpful.

A patient with organic heart disease is subject to special emotional stress. When the diagnosis of heart disease is made, the patient must be given full, frank, and optimistic explanations. Most people can face facts better than they can the unknown.

(Presented at the Bingham Associates Program for Postgraduate Medical Education, Boston, Jan. 14, 1957.)

Strictures of the Esophagus

San Juan, Puerto Rico.—Five patients with extensive stricture of the esophagus were treated at the University of Puerto Rico School of Medicine by substituting a loop of intestine (jejunum or colon) placed behind the sternum for the narrowed esophagus, and anastomosing or joining the intestine to the esophagus at the neck or to the pharynx, report Gumersindo Blanco and Alberto Adam. With this operation there is complete gastric by-pass.

Before this operation, these patients had been unable to swallow for many years, following ingestion of hydrochloric acid. Maintenance of nutrition was accomplished by means of a rubber tube placed through the abdomen into the stomach. After retrosternal esophagojejunostomy, all patients were able to swallow food without difficulty. No strictures or pulmonary complications developed, and all patients are now able to lead a normal life.

(Presented before the American College of Surgeons, Sectional Meeting, San Juan, Puerto Rico, Jan. 16–18, 1957.)

Advances in Roentgen-Ray Diagnosis of Diseases of the Esophagus

Berlin, Germany.—As the human eye is too slow to catch all pathologic changes that show during barium contrast studies of the esophagus with the fluoroscope, the Metzner camera, which gives about 30 exposures/second, was formerly used in his department, reports Hermann Westerkamp (Radiologist, Neukoelln Hospital, Berlin). However, a considerable amount of radiation was necessary to get at least fair pictures, especially in the upper third. Patients got as much as 50 r during a 10 second examination. During the last few months, a system has been used in which a roentgen-ray machine, an intensifying screen, and a movie camera are combined. This screen intensifies the picture 800 times. With a quantity of radiation not exceeding that of a fluoroscopic examination (4 to 6 r), good movies have thus been made of the swallowing act in patients with cardiospasm, carcinoma, and diverticula, allowing considerable accuracy in the roentgen-ray diagnosis of these conditions.

(Presented before the staff conference at Neukoelln Hospital, Berlin, Germany, Feb. 14, 1957.)

Papanicolaou Smear Test

Denver, Colo.—A Papanicolaou smear test given 12,000 supposedly healthy women in Denver during a nine year period disclosed 52 cases of cervical cancer in the preclinical stage, reports E. Stewart Taylor (University of Colorado Medical School). If it had not been for this extremely early screening of supposedly normal persons, it would have been at least five years before many of the cancers could be discovered, Dr. Taylor estimates. Then, in many cases, the disease would have been too far advanced to save the patient. But since they were discovered so early, the tumors were easy to treat, and indications were that no further cancers would develop. Dr. Taylor indicates that wide use of the test among apparently healthy women could save many lives.

(Presented before the annual meeting of the Obstetrical and Gynecological Assembly of Southern California, Los Angeles, Feb. 15, 1957.)

Evaluation of the Hardy-Wolff-Goodell Pain Threshold Apparatus and Technique: Review of the Literature

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